Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-018-5001-4

GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

The reproducibility of the novel utilization of five-dimensional ultrasound and power Doppler in the prediction of endometrial receptivity in intracytoplasmic sperm-injected women: a pilot prospective clinical study

M. Elsokkary[1] · A. Bahaa Eldin[1] · M. Abdelhafez[1] · A. Rateb[1] · M. Samy[1] · A. Eldorf[2] · B. A. Islam[1] · T. A. Raafat[1] · I. A. Gomaa[1] · M. Taema[1] · R. Mohamed[1] · M. Elshourbagy[1] · W. Tawfik[3] · A. Morad[3] · M. Mostafa[1] · A. Abbas[1] · T. Assar[3] · H. Hemeda[1]

Received: 14 May 2018 / Accepted: 4 December 2018

Abstract

Objective The ultimate goal of this study is to reassess the five-dimensional implantation markers and pregnancy predictors on the day of human chorionic gonadotropin injection in the intracytoplasmic sperm injection and embryo transfer programs.

Design A pilot prospective clinical trial.

Setting The Assisted Reproductive Technology Unit of Ain Shams Maternity Teaching Hospital during the period from April 2014 to December 2017.

Patients and methods The study was conducted on 400 women undergoing intracytoplasmic sperm injection (ICSI). Those women were not older than 40 years, with normal uterine cavity and with no previous uterine scars.

Intervention The ovarian stimulation protocol, used in this study for all patients, was the long protocol, before ovarian stimulation therapy, patients were instructed to use oral contraceptive pills from day 2 starting in the preceding cycle, then the standard regimen. On the day of hCG administration, 5D transvaginal ultrasound measurements were performed by the same observer after the patients had emptied their bladders. Measurements included endometrial volume and 3D power Doppler parameters, endometrial vascularization index, flow index, and vascularization flow index.

Results The present study shows that endometrial volume ≥ 5 in the prediction of endometrial receptivity in ICSI patients had good sensitivity and low specificity in a group application; in an individual application it had good predictive negative value and bad predictive positive value. So it could be used as a good test to exclude success. Overall pregnancy rate was 40.5%; endometrial volume, flow index, vascularization index, and vascularization flow index were significantly lower in the nonpregnant group than those of the pregnant group. The area under curve in the receiver operating characteristic for three-dimensional ultrasound and power Doppler angiography parameters was statistically significant, but their values were suggestive but not conclusive in the prediction of endometrial receptivity in ICSI patients, no cutoff points with good diagnostic characteristics could be obtained.

Conclusion Five-dimensional ultrasound and power Doppler angiography is a useful exam to assess the endometrial receptivity in IVF/ICSI and embryo transfer cycles.

Keywords Five-dimensional ultrasound · Doppler · Receptivity · ICSI

✉ M. Elsokkary
mohammedelsokkary1@yahoo.com

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Abbasyia, Cairo, Egypt

[2] Department of Obstetrics and Gynecology, Tanta University, Tanta, Egypt

[3] Department of Obstetrics and Gynecology, Banha University, Banha, Egypt

Introduction

The methods employed in assisted reproductive technologies (ART) have advanced significantly since 1978; the first in vitro fertilization (IVF) birth. Techniques are currently available that make it possible to select excellent embryos and to evaluate the endometrial receptivity. Moreover, ART

Published online: 19 December 2018

protocols continue uninterruptedly to develop with the goal of reaching better pregnancy outcomes, less multiple births, and healthy infants from genetically affected ancestors. Nevertheless,* in spite of these achievements, implantation rates are still till now relatively not high and have not elevated considerably in the past few years. This proposes that pregnancy outcomes in stimulated cycles are still suboptimal [1]. Successful blastocyst implantation is an important event in assisted and natural reproduction. Embryo implantation is a dynamic series of events, including embryo adherence, attachment to the endometrial receptors, and finally invading the endometrial stroma [2]. Implantation failures could happen due to many reasons [3], involving poor quality of the embryos which is identified as a crucial reason of failures [4].

Another major acknowledged cause for successful embryo implantation is an unreceptive endometrium. It is well known that blastocysts cannot adhere to an immature endometrium [2] which could result in an ineffective implantation in spite of the transfer of "good quality" embryos. In addition, successful implantation further depends on the cross talk between the blastocyst and a properly matured endometrium [2].

Endometrial receptivity could be assessed by detailed histological evaluation of an endometrial biopsy, proteins in endometrial wash [5] or more widely by ultrasonographic evaluation of the endometrial pattern [6].

It is evident that vascularization performs a crucial share in different human reproductive functions as follicular maturation, development of corpus luteum, endometrial maturation and ultimately implantation [7]. For that cause most of the studies had paid utmost importance to ovarian and endometrial angiogenesis for anticipating outcome in ART programs [8].

Endometrial angiogenesis means adequate endometrial receptivity as the endometrium is the place of embryonic implantation [9]. Inadequate color Doppler mapping at the endometrial and subendometrial levels is linked to a considerable decline in the pregnancy rate, while the implantation rate elevates when vessels could be visualized reaching the subendometrial halo and the endometrium [10].

Endometrial ultrasound indices and the assessment of uterine and endometrial blood flow had long been studied as implantation markers in ART and embryo transfer cycles [9]. Moreover, when utilized as ART pregnancy predictors, their results are questionable [6]. A triple-layer endometrial pattern and an endometrial thickness more than 7 mm have been suggested as the markers of endometrial receptivity but had produced a high percentage of false-positive results [6].

Five-dimensional ultrasound and power Doppler angiography (5D US-PDA) has the advantage of measuring both the endometrial blood flow and endometrial volume (EV). And its utilization in the study of endometrial receptivity exhibits high intraobserver and interobserver reproducibility for all the ultrasound and 5D Doppler indices. The aim of this study is to assess the 5D US-PDA indices as possible implantation markers and for pregnancy prediction on the day of hCG intake in an ICSI and embryo transfer program.

Patients and methods

The study was done in the Assisted Reproduction Unit of Ain Shams University hospital during the period from April 2014 to December 2017. A pilot prospective clinical study was performed on infertile patients undergoing IVF/ICSI cycle, because of male factor or tubal factor.

Epi Info program was used for the calculation of sample size guided by:

- Power of the test = 80%,
- Confidence level = 95%,
- Alfa error = 5%.
- Total sample: 400 infertile patients.

Exclusion criteria: those who passed 40 years of age, women with history of uterine surgery affecting the endometrium such as submucous myomectomy, those with obvious uterine pathology as synechia or endometrial polyp, also women with basal follicle stimulating hormone (FSH) of more than 10 mIU/mL were not included in the study. This study conformed to the declaration of Helsinki for ethical medical research. Institutional review of Faculty of Medicine, Ain Shams University and ethical board approval (4th Jan 2014) were obtained and all participants signed informed written consents.

Long protocol of ovarian stimulation regimen was offered for all patients who participated in this study according to the protocol applied in the unit starting from the preceding cycle using oral contraceptive pills, pituitary suppression by decapeptyl followed by ovarian stimulation with human menopausal gonadotropins in individualized dose according to age, body mass index, number of antral follicles, ovarian response in previous attempt, and hormonal profile. Serial transvaginal ultrasound examination to monitor the size and number of developing follicles was done, maturation was triggered by 10,000 IU of human chorionic gonadotropin (hCG) when at least three dominant follicles greater than 18 mm are confirmed. Five-dimensional ultrasonography and power Doppler angiography scans and measurements were performed using UGEO WS80A Samsung Medison Ultrasound system on the day of (hCG) administration using VOCAL (virtual organ computer-aided analysis). Measurements included the endometrial volume (EV) and five angiographic power Doppler indexes: vascularization index (VI), flow index (FI), and vascularization flow index (VFI),

which represent the number of vessels, blood flow, and endometrial perfusion, respectively. The VOCAL program calculates automatically the EV and five angiographic power Doppler indexes: (VI), (FI), and (VFI) [11]. Ovum pickup was done under general anesthesia 34–36 h after hCG injection. Oocytes were fertilized by ICSI according to the unit protocol, and embryos were transferred after 2 days (day 2 embryo transfer), progesterone was used for luteal phase support. Although the number of transferred embryos is determined by many factors such as, the age of patient, previous IVF failure, and the number of embryos available, we included those patients who ended with transfer of at least two good quality embryos, grade 1 and grade 2 (i.e., > 20% embryo fragmentation), this is to limit the embryo cause of implantation failure. Pregnancy was confirmed by quantification of the serum (hCG) level 14 days after embryo transfer.

Statistical methodology

Retrieved data were recorded on an investigative report form. The data were analyzed with SPSS® for Windows®, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in the form of mean, standard deviation (SD), and range. Description of qualitative (categorical) data was performed in the form of numbers and percent. The analysis of numerical variables was performed using Student's unpaired *t* test (for two groups) or ANOVA (for more than two groups). The analysis of categorical data was performed using Fischer's exact test and Chi-squared test. Significance level was set at 0.05.

Results

Table 1 shows that age and BMI were higher in nonpregnant group than those in pregnant group, but the difference was statistically nonsignificant. Also there was no significant difference between nonpregnant and pregnant cases regarding past history, duration, type and etiology of infertility, and having previous ICSI. E2 was significantly higher in cases with nonpregnant group than those with pregnant group. There was no significant difference between nonpregnant and pregnant cases regarding FSH, LH, prolactin, number, grade of transferred embryos, and endometrial pattern. Endometrial volume, flow index, vascularization index, and vascularization flow index were significantly lower in cases with nonpregnant group than those with pregnant group.

Overall pregnancy rate was 40.5%, endometrial volume ≥ 5 in the prediction of endometrial receptivity in ICSI patients had good sensitivity and low specificity in a group application; in an individual application it had good predictive negative value and bad predictive positive value. So it could be used as a good test to exclude success.

The area under curve in the receiver operating characteristic (ROC) for three-dimensional ultrasound and power Doppler angiography parameters was statistically significant, but their values were suggestive and not conclusive in the prediction of endometrial receptivity in ICSI Patients (no cutoff points with good diagnostic characteristics could be obtained) (Fig. 1).

Table 2 and Fig. 2 show that the area under curve in the receiver operating characteristic (ROC) for five-dimensional ultrasound and power Doppler angiography parameters was statistically significant, but their values were suggestive and not conclusive in the prediction of endometrial receptivity in ICSI patients (i.e., no cutoff points with good diagnostic characteristics could be obtained) except endometrial volume had a good value.

Table 3 and Fig. 3 show that endometrial volume ≥ 5 in the prediction of endometrial receptivity in ICSI patients had good sensitivity and low specificity in a group application; in an individual application it had good predictive negative value and bad predictive positive value. So it could be used as a good test to exclude success.

Discussion

The pregnancy potential of high quality embryos is still not high during IVF/ET programs, in spite of the progresses in the programs of ovarian stimulation, the technique of ART and better recent cultures; implantation failure is still a real obstacle in reproductive medicine [13]. Implantation relies upon a cross talk between the embryo and the good quality endometrium various strategies had been innovated to assess endometrial receptivity, like the histologic dating of an endometrial sampling [14], cytokines in uterine washes [15], genomic map of endometrial sample [16] or more commonly utilized ultrasound study of the endometrium.

Angiogenesis has a major share in different female reproductive processes such as the recruitment of a dominant follicle, development of a corpus luteum, receptivity of endometrium, and subsequent implantation [17, 18].

A sufficient blood supply in the endometrium is needed for the successful implantation. Gannon et al. [19] assessed the endometrial microvascular blood flow utilizing an intrauterine laser Doppler and demonstrated a real rise in vascularity during early follicular and luteal phases.

Endometrial blood flow was assessed in 75 infertile women by the intrauterine laser Doppler between day 4 and 6 of the luteal phase of a natural cycle before IVF and was found to be better than endometrial thickness, uterine pulsatility index (PI), and the histologic dating of the endometrium in predicting endometrial receptivity [20]. Prediction

Table 1 Comparison between nonpregnant and pregnant cases

	Not pregnant ($N=238$)	Pregnant ($N=162$)	P
Age (years)	31.1 ± 1.8	30.2 ± 2.4	> 0.05
BMI (kg/m^2)	30.1 ± 4.3	30.5 ± 4.2	> 0.05
Laparoscopy	160 (67.2%)	112 (69.1%)	> 0.05
Laparotomy	66 (27.7%)	43 (26.5%)	> 0.05
Appendectomy	46 (19.3%)	30 (18.5%)	> 0.05
D&C	59 (24.8%)	41 (25.3)	> 0.05
Irrelevant	77 (32.4%)	54 (33.3%)	> 0.05
Duration of infertility (years)	8.1 ± 1.2	7.9 ± 2.3	> 0.05
Type			
1ry	146 (61.3%)	101 (62.3%)	> 0.05
2ry	92 (38.7%)	61 (37.7)	
Etiology			
Tubal	133 (55.9%)	91 (56.1%)	> 0.05
Male	105 (44.1%)	71 (43.9%)	
Previous ICSI			
No	201 (84.5%)	137 (84.6%)	> 0.05
Yes	37 (15.5%)	25 (15.6%)	
E2 (pg/mL) day 3	39.1 ± 8.6	29.9 ± 13.6	< 0.05
FSH (mIU/mL)	7.2 ± 1.9	6.9 ± 1.8	> 0.05
LH (mIU/mL)	4.8 ± 3.1	5.2 ± 1.9	> 0.05
Prolactin (ng/mL)	13.2 ± 3.8	12.9 ± 4.1	> 0.05
Number of embryos			
Two	57.9%	56.5%	> 0.05
Three	42.1%	43.5%	
Grade of embryos			
A1	74.9%	76.1%	> 0.05
A2	25.1%	23.9%	
Endometrial volume (mL)	4.2 ± 2.5	6.5 ± 1.9	<0.001
Flow Index (0–100)	22.8 ± 3.2	26.1 ± 2.3	< 0.05
Vascularization index %	16.8 ± 2.6	19.1 ± 2.9	< 0.05
Vascularization flow index (0–100)	3.1 ± 1.1	4.9 ± 3.1	< 0.05
Endometrial pattern			
Triple line	53%	52%	> 0.05
Non-triple line	47%	48%	

of pregnancy was more in women with endometrial blood flow of equal to or more than 29 mL/min per 100 g of tissue than in women with lower values (42% versus 15%, respectively, $P < 0.05$).

Endometrial blood flow can be assessed by two-dimensional (2D) or (3D) ultrasound with color and power Doppler. Power Doppler is more sensitive than color Doppler at detecting low velocity flow and hence improves the visualization of tiny vessels [21].

Kupesic and Kurjak [22] first declared endometrial blood flow assessed by transvaginal color Doppler technique during the periovulatory phase. However, the results were not correlated with the pregnancy rate in the study [22].

Endometrial and subendometrial blood flows evaluated by color and power Doppler were correlated with the conception rates during IVF programs. It is apparent that 2D Doppler flow markers of spiral arteries as PI and PSV are not significantly suggestive of conception [23], although Battaglia et al. [24] and Kupesic et al. [25] demonstrated lower spiral artery PI in pregnant cycles than in nonpregnant ones.

The current study demonstrated that we can evaluate simultaneously the endometrial morphologic characters, EV, and endometrial vascularization by the 5D power Doppler markers. Our study showed that the best intraclass correlation markers to evaluate the EV and endometrial vascularity markers with the VOCAL technique could be reached working in the coronal or "C" plane with a rotational angle of 9° and this method agreed with Merce et al. [11].

We did not find statistically significant differences in the endometrial pattern between the pregnant and nonpregnant

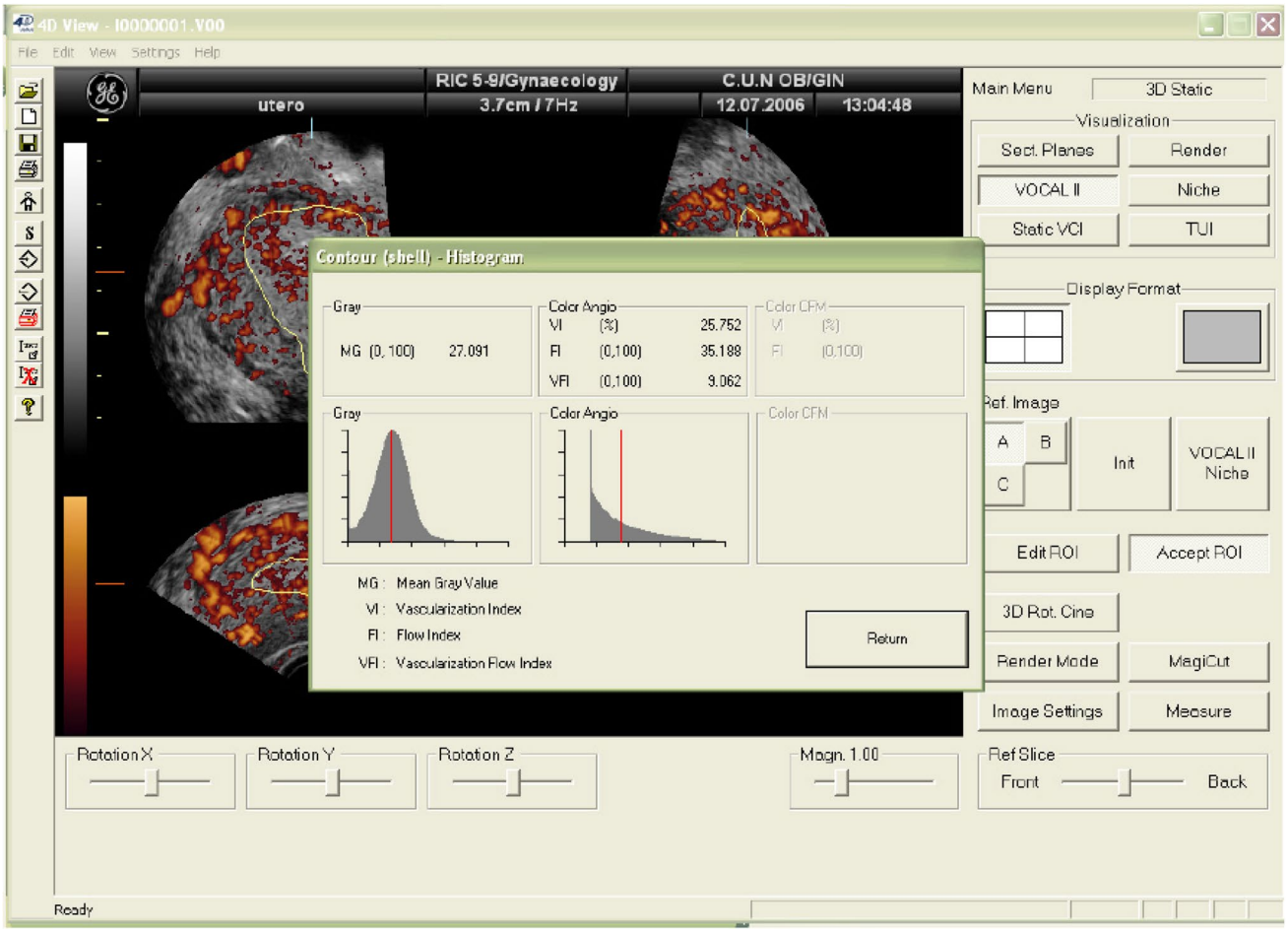

Fig. 1 5D-power Doppler indexes for assessing endometrial vascularization by means of the three-dimensional ultrasound [12]

Table 2 Value of three-dimensional ultrasound and power Doppler angiography parameters in the prediction of endometrial receptivity in ICSI patients

	AUC	SE	*P*	95% CI	
Endometrial volume (mL)	0.712	0.082	< 0.05*	0.582	0.833
Flow Index (0–100)	0.814	0.091	< 0.05*	0.721	0.881
Vascularization index %	0.543	0.072	> 0.05	0.391	0.786
Vascularization flow index (0–100)	0.711	0.070	< 0.05*	0.592	0.856

AUC area under the curve, *SE* standard error, *CI* confidence interval

*Significant if *P* value < 0.05

groups. However, the EV was statistically significantly higher in women who got pregnant. However, previous studies could not find that the EV is suggestive for pregnancy and this might be explained by technical differences in the volume calculation [26]. Studies from Kupesic et al. [25] and Wu et al. [27] assessed the EV by a nonrotational technique, whereas Järvelä et al. [28] and Ng et al. [26]

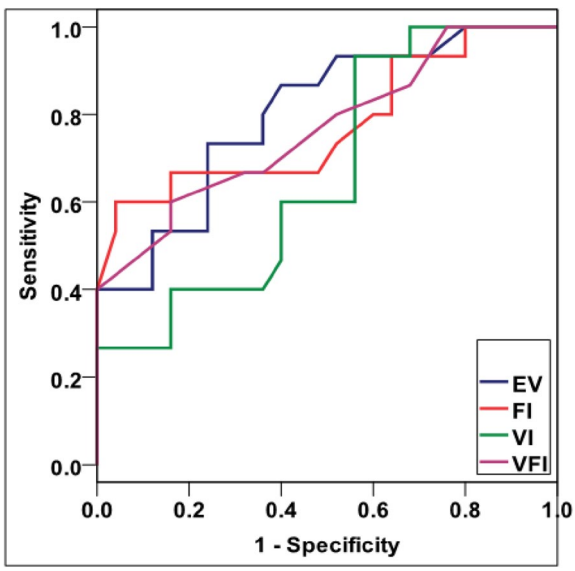

Fig. 2 ROC curve for endometrial volume, flow index, vascularization index, and vascularization flow index in the prediction of endometrial receptivity in ICSI patients

Table 3 Evaluation of endometrial volume ≥ 5 mL in the prediction of endometrial receptivity in ICSI patients

Character	Value (%)
Sensitivity	85.0
Specificity	69.0
Predictive positive value	81.1
Predictive negative value	90.1
Diagnostic accuracy	75.0

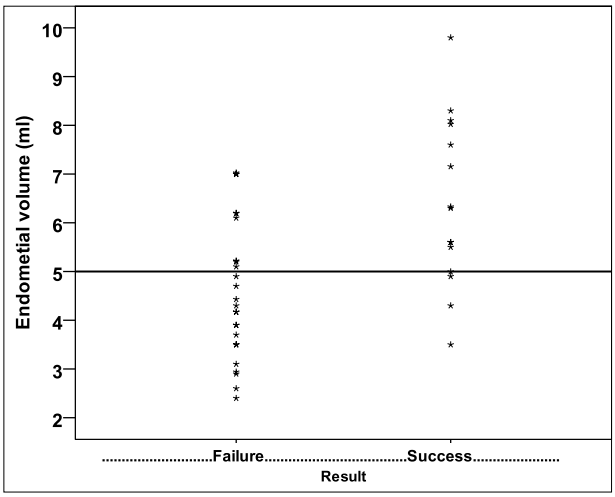

Fig. 3 Evaluation of endometrial volume (≥5 mL) in the prediction of endometrial receptivity in ICSI patients

applied the VOCAL technique but delineated and assessed fewer planes than we make to calculate the EV.

Although the vast majority of researchers had evaluated subendometrial vascularization as a conception predictor [26–28], we selected to calculate only the 5D power Doppler markers of the endometrium. Our decision was relied on the fact that subendometrial vascularization experiences the same alterations as the endometrial but with higher vascularity markers [29]. As it is impossible to evaluate the subendometrial space precisely, it has been defined as an outer shell around the endometrium with many different thicknesses such as 10 mm [28], 5 mm [25], or 1 mm [26]. The endometrial thickness differs from women to another, so if we used the same shell thickness, the vessels involved in the subendometrial zone will vary from patient to patient, reducing the reliability of the results.

The results of the present study were in agreement with results of Merce et al. [11] in which they evaluated 80 women who underwent IVF cycles using endometrial 3D US-PDA assessed by VOCAL to confirm whether endometrial parameters by 3D US-PDA can predict implantation rate, the results demonstrated that, in the pregnant group, EV, FI, and VFI were statistically significantly higher. In the current study, the area under receiver operating characteristic (ROC) curve was statistically significant for EV (0.803), FI (0.775), and VFI (0.768), whereas for VI there was no statistically significant difference between pregnant and nonpregnant group VI (0.668).

The present study was partially in agreement with the results of Wu et al. [27] who evaluated endometrial and subendometrial blood flow on the day of hCG in 54 patients. Endometrial VFI on the day of hCG was significantly more in the pregnant group while endometrial VI and FI were the same between pregnant and nonpregnant cycles.

The results of the present study were also partially in agreement with Kupesic et al. [25], in which 3D US was done on the day of embryo transfer, i.e., 5 days after oocyte retrieval. Endometrial and subendometrial FI were significantly more in pregnant cycles while endometrial and subendometrial VI and VFI were similar between pregnant and nonpregnant patients, and those results contradicted the results of the present study.

However, Kupesic et al. [25] and Wu et al. [27] found that subendometrial vascularity markers are the predictive factors for conception on the day of transfer and on the day of hCG intake, respectively. On the other hand, Järvelä et al. [28] and Ng et al. [26] did not confirm the 3D power Doppler markers to be good predictors for conception after FSH stimulation [28] or on the oocyte retrieval day [26].

Järvelä assessed endometrial and subendometrial vascularization by 3D PDA in 35 women undergoing IVF [28]. It was done twice, one after FSH stimulation but before hCG intake and a second time on the day of oocyte retrieval (36 h after hCG intake). They utilized the VOCAL with a 15- rotation step. They described the subendometrial region as the region 10 mm beneath myometrial endometrial junction. Conception rate was 37%. They did not find differences on endometrial and subendometrial vascularization between pregnant and nonpregnant cycles. But, they demonstrated that endometrial and subendometrial VI were reduced significantly between the two examinations, this finding might be in agreement with the findings of Raine-Fenning in natural cycles, who declared a reduction of endometrial vascularity during the periovulatory period [29].

Ng evaluated endometrial and subendometrial 3D-PDA markers in 525 women undergoing the first IVF cycle [26]. Ultimately 451 cycles were eligible and conception rate in this series was 20.8%. They utilized the VOCAL with 15-rotation step. Subendometrial area was considered to be within 1 mm of the originally described myometrial–endometrial contour. Ultrasound was done on the day of oocyte retrieval. They found that patients in the pregnant group had significantly reduced endometrial VI and VFI than those in the nonpregnant group. Endometrial FI and subendometrial VI, FI, and VFI were the same. Multiple logistic regression

analysis showed that from multiple parameters only the number of embryos got replaced and endometrial VI significantly increased the chance of conception, but this latter had only a marginal predictive value (odd ratio: 0.87, 95% CI 0.76–0.99).

Conclusion and recommendations

In view of such findings, 5D US has been considered as a promising tool for assessing the endometrial receptivity; but the results are still debatable due to multiple techniques differences, especially in the date of the cycle when examinations occurred and the VOCAL indices. Other factors include the differences in the population under study and the protocols of stimulation and embryo transfer. We consider the results of our study as interesting, and hope that future studies can prove our findings. In this context, we believe that the innovative use of 5D markers of endometrial receptivity is useful for selecting the more suitable cycle for the embryo transfer. Five-dimensional US and power Doppler angiography is very helpful in assessing the endometrial receptivity in IVF/ICSI and embryo transfer programs. The EV and 5D power Doppler markers on the day of hCG intake can predict conception, especially when no grade 1 or only one grade 1 embryo is to be transferred. These results may have a clinical application in programs with single-embryo transfer programs.

Acknowledgements Special thanks go to the patients and their families for the great support of our work. Also, the authors highly appreciate the support from fetology unit of Ain Shams University Maternity Hospital for the outstanding support during the entire experiment.

Author contributions All authors had put the plan, collected the data, participated in the surgical procedure and follow-up of the patients.

Funding No available funding.

Compliances with ethical standards

Ethical consideration Institutional review board (IRB) approval: the protocol was discussed by the ethical scientific committee and informed consent was taken before the participation.

Subject confidentiality All evaluation forms, reports, laboratory specimens, and other records that leave the site would not comprise unique personal data to maintain subject confidentiality.

Consent procedure The investigator made a great concern that a correct informed consent process was in place to make sure that potential research subjects were fully addressed about the nature and objectives of this clinical trial, the potential hazards and gains of study participation, and also their rights as research subjects. The investigator took the written, signed informed consent of each participant before performing any study-specific technique on the participant. The investigator retained the forms of original signed informed consents. All data and materials are available on request with an agreement for publication.

Conflict of interest All the authors declare no conflict of interest.

References

1. Andersen AN, Gianaroli L, Felberbaum R, de Mouzon J, Nygren KG (2005) Assisted reproductive technology in Europe, 2001. Results generated from European registers by ESHRE. Hum Reprod 20:1158–1176
2. Achache H, Revel A (2006) Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod 12(6):731–746
3. Levi Setti PE, Colombo GV, Savasi V, Bulletti C, Albani E, Ferrazzi E (2004) Implantation failure in assisted reproduction technology and a critical approach to treatment. Ann N Y Acad Sci 1034:184–199
4. Urman B, Yakin K, Balaban B (2005) Recurrent implantation failure in assisted reproduction: how to counsel and manage. A. General considerations and treatment options that may benefit the couple. Reprod Biomed Online 11:371–381
5. Li TC, MacKenna A, Roberts R (1993) The techniques and complications of out-patient uterine washing in the assessment of endometrial function. Hum Reprod 8:343–346
6. Friedler S, Schenker JG, Herman A, Lewin A (1996) The role of ultrasonography in the evaluation of endometrial receptivity following assisted reproduction treatments: a critical review. Hum Reprod 2:323–335
7. Demir R, Kayisli UA, Cayli S, Hupperzt B (2006) Sequential steps during vasculogenesis and angiogenesis in the very early human placenta. Placenta 27:535–539
8. Tekay A, Martikainen H, Jouppila P (2006) Blood flow changes in uterine and ovarian vasculature, and predictive value of transvaginal pulsed colour Doppler ultrasonography in an in vitro fertilization programme. Hum Reprod 10:688–693
9. Merce LT (2002) Ultrasound markers of implantation. Ultrasound Rev Obstet Gynecol 2:110–123
10. Chien LW, Au HK, Chen PL, Xiao J, Tzeng CR (2002) Assessment of uterine receptivity by the endometrial-subendometrial blood flow distribution pattern in women undergoing in vitro fertilization-embryo transfer. Fertil Steril 78:245–251
11. Merce Luis T, Barco Maria J, Bau Santiago, Troyano Juan (2008) Are endometrial parameters by three-dimensional ultrasound and power Doppler angiography related to in vitro fertilization/embryo transfer outcome? Fertil Steril 89:112–117
12. Alcāzar JL (2006) Three-dimensional ultrasound in gynecology: current status and future perspectives. Curr Women's Health Rev 1:1–14
13. De los Santos MJ, Mercader A, Galan A, Albert C, Romero JL, Pellicer A (2003) Implantation rates after two, three, or five days of embryo culture. Placenta 24:13–19
14. Noyes RW, Haman JO (1953) Accuracy of endometrial dating; correlation of endometrial dating with basal body temperature and menses. Fertil Steril 4:504–517
15. Lédé-Bataille N, Laprée-Delage G, Taupin JL et al (2002) Concentration of leukaemia inhibitory factor (LIF) in uterine flushing fluid is highly predictive of embryo implantation. Hum Reprod 17:213–218
16. Horcajadas JA, Pellicer A, Simon C (2007) Wide genomic analysis of human endometrial receptivity: new times, new opportunities. Hum Reprod Update 13:77–86

17. Abulafia O, Sherer DM (2000) Angiogenesis of the ovary. Am J Obstet Gynecol 182:240–246
18. Smith SK (2001) Angiogenesis and reproduction. Br J Obstet Gynaecol 108:777–783
19. Gannon BJ, Carati CJ, Verco CJ (1997) Endometrial perfusion across the normal human menstrual cycle assessed by laser Doppler fluxmetry. Hum Reprod 12:132–139
20. Jinno M, Ozaki T, Iwashita M et al (2001) Measurement of endometrial tissue blood flow: a novel way to assess uterine receptivity for implantation. Fertil Steril 76:1168–1174
21. Guerriero S, Ajossa S, Lai MP et al (1999) Clinical applications of colour Doppler energy imaging in the female reproductive tract and pregnancy. Hum Reprod Update 5:515–529
22. Kupesic S, Kurjak A (1993) Uterine and ovarian perfusion during periovulatory period assessed by transvaginal color Doppler. Fertil Steril 60:439–443
23. Zaidi J, Campbell S, Pittrof FR et al (1995) Endometrial thickness morphology, vascular penetration and velocimetry in predicting implantation in an IVF program. Ultrasound Obstet Gynecol 6:191–198
24. Battaglia C, Artini PG, Giulini S et al (1997) Colour Doppler changes and thromboxane production after ovarian stimulation with gonadotrophin- releasing hormone agonist. Hum Reprod 12:2477–2482
25. Kupesic S, Bekavac I, Bjelos D, Kurjak A (2001) Assessment of endometrial receptivity by transvaginal color Doppler and threedimensional power Doppler ultrasonography in patients undergoing in vitro fertilization procedures. J Ultrasound Med 20:125–134
26. Ng EH, Chan CC, Tang OS, Yeung WS, Ho PC (2006) The role of endometrial and subendometrial blood flows measured by threedimensional power Doppler ultrasound in the prediction of pregnancy during IVF treatment. Hum Reprod 21:164–170
27. Wu HM, Chiang CH, Huang HY, Chao AS, Wang HS, Soong YK (2003) Detection of the subendometrial vascularization flow index by three-dimensional ultrasound may be useful for predicting the pregnancy rate for patients undergoing in vitro fertilization-embryo transfer. Fertil Steril 79:507–511
28. Jarvela IY, Sladkevicius P, Kelly S, Ojha K, Campbell S, Nargund G (2005) Evaluation of endometrial receptivity during in vitro fertilization using three-dimensional power Doppler ultrasound. Ultrasound Obstet Gynecol 26:765–769
29. Raine-Fenning NJ, Campbell BK, Clewes JS, Kendall NR, Johnson IR (2004) Defining endometrial growth during the menstrual cycle with three-dimensional ultrasound. BJOG 111:944–949