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Endometrial spatio-temporal image correlation (STIC) and prediction of outcome following assisted reproductive treatment

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ABSTRACT

Objective: The aim of this study was to correlate manual and spherical endometrial spatio-temporal image correlation (STIC) vascularity indices with assisted reproductive treatment (ART) outcomes.
Study design: STIC ultrasound assessments of the endometrium were carried out at three time-points in 127 women in a prospective observational study.
Results: Biochemical pregnancy rate was 69% (88/127), with a biochemical and clinical pregnancy loss of 17%. Endometrial STIC vascularity indices in the assessed time-points did not differ between subjects who achieved a clinical pregnancy and those who did not ($P > 0.05$). For first trimester miscarriage, minimal manual vascularization index (VI) at oocyte collection (cut-off value $\geq$0.7; sensitivity 80.0% and specificity 68.1%) demonstrated the highest area under the curve (AUC) of 0.8.
Conclusion: In summary, STIC modality is not a useful tool to predict ART outcome, however manual STIC analysis of endometrial vascularity seems to be more accurate in predicting first trimester pregnancy loss.

Introduction

Spatio-temporal image correlation (STIC) is an ultrasound modality allowing for assessment of blood flow characteristics throughout the entire cardiac cycle within a given volume of interest (VOI). STIC acquisition is an automated process, where the transducer array records a volume consisting of numerous 3D volumes, with a very high recorded B-mode frame rate (up to 150 frames/s) [1]. Combination of this technology with power Doppler (PD) imaging allows for acquisition of a series of three-dimensional (3D) PD volumes, each representing a different phase of the cardiac cycle [2–4]. This is displayed as a cine loop, which can be stopped at any time allowing for detailed analysis of the single volume. Therefore, each volume contained within a single power Doppler STIC (PDSTIC) acquisition produces a vascularization index (VI), flow index (FI) and vascularization flow index (VFI) representing the intensity of Doppler signal correlated with blood flow [5,6]. As expected, the vascularity assessed using STIC is greater during cardiac systole than diastole with significantly different vascular index values [3,7].

Previously, only a small fragment of the endometrium, placenta or ovarian stroma using spherical VOI STIC sampling was possible [3,7,8], but advancements in currently available ultrasound equipment allow for an angle of acquisition $\geq$90°, which is necessary for inclusion of the entire endometrium. Due to the acquisition time (15 s), excessive respiratory movement or transmitted pulsatility from the iliac vessels can induce motion artifacts distorting the image and limit the number of good quality images appropriate for analysis [3]. As some planes are computer-generated reconstructions, analysis of these can be troublesome or even impossible due to blurriness of planes.

Description of endometrial vascularity assessed by 3DPD sonography, which averages the Doppler signal intensity over

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the duration of acquisition, has been found to be positively correlated with assisted reproductive treatment (ART) outcome by some authors [9–12]. We postulated that the ability to obtain a more accurate description of blood flow through the application of STIC would aid the prediction of ART outcome. To test this hypothesis, we performed spherical and manual STIC analysis of vascularity in the mid-luteal endometrium in the cycle preceding ART, assessment on day of transvaginal oocyte retrieval (TVOR) and on day of embryo transfer (ET). The obtained vascularity indices were then assessed as markers to predict ART outcome.

Materials and methods

Study design

The study was designed as a single center, prospective observational cohort study carried out in a university affiliated infertility treatment clinic. Local research ethics committee approval was granted (12/EM/0345). Women prior to undergoing IVF or ICSI treatment underwent a mid-luteal phase ultrasound assessment, assessments on day of TVOR and ET. Recruitment to the study took place from February 2013 to July 2014.

Participants and collected data

All women under the age of 49 with no major congenital or acquired uterine anomaly precluding endometrial assessment undergoing in vitro fertilization (IVF), intra-cytoplasmic sperm injection (ICSI) or frozen embryo transfer (FET) using own oocytes were eligible. The sample size was based on the recruitment period available for the study. Following written consent all participants underwent a mid-luteal transvaginal ultrasound (TVUS) scan and IVF or ICSI treatments using standard agonist or antagonist protocols. In brief: during a long protocol, pituitary down-regulation with gonadotropin releasing hormone (GnRH) agonist, Buserelin (Aventis Pharma, Kent, UK) starts 7 days prior to the expected date of next menstrual bleed. Down regulation was confirmed 2 weeks later by presence of quiescent ovaries with follicles $<$10 mm diameter, endometrium $\leq$5 mm in thickness and serum estradiol level $<$200 pmol/l. Ovarian stimulation was commenced subsequently. In a short antagonist protocol, stimulating medications (Menpur or Gonal-F) were commenced on day 2 of period with a GnRH antagonist, cetrorelix (Cetrotide, Merck Serono, UK), commenced when a lead follicle began to develop. Starting doses of gonadotrophins [human menopausal gonadotropin (HMG, Menopur, Ferring, UK) or recombinant FSH-follitropin α (Gonal-F, Merck Serono, UK)] were 150–450 iu based on patients' characteristics. When criteria for oocyte retrieval were met ($\geq$3 leading follicles are $\geq$17 mm), 250 μg of choriogonadotrophin α (Ovitrelle, Merck Serono, UK), was administered subcutaneously to trigger oocyte maturation. TVOR was performed 36 h later directly preceded by ultrasound assessment of the endometrium.

Depending on the number of oocytes, the fertilization rate and number of day 2 embryos, one or two embryos were transferred on day 2, 3 or 5. Micronized progesterone (Cyclogest, 400 μg twice daily) administered vaginally was used as luteal support continued until pregnancy test date, or until 10th week of gestation if pregnancy occurred.

Outcome variables

Demographic data obtained included participant's age and past reproductive history. Sonographic data included endometrial pattern, thickness, volume, and STIC vascularity indices. The main outcome of this study was clinical pregnancy in study subjects, defined by the presence of a fetal heartbeat at 6 weeks gestation. A biochemical pregnancy was defined as a positive urinary pregnancy test 14 days after ET. Biochemical pregnancy loss was defined as no evidence of pregnancy at the 6-week ultrasound scan following a positive pregnancy test. Miscarriage was defined as absence of fetal heartbeat on the scan following prior visualization of fetal cardiac activity. Ongoing pregnancy was defined as a viable pregnancy past the 12th week of gestation.

Image acquisition and analysis

Ultrasound assessments were performed using a Voluson E8 Expert BT12 (GE Healthcare, Zipf, Austria) and 5–9 MHz endovaginal transducer 7–9 days following luteinizing hormone (LH) surge as detected by urinary test, or day 21 $\pm$ 2 in case of absent LH surge in the cycle preceding controlled ovarian hyperstimulation (COH); 36 h after human chorionic gonadotropin (hCG) injection (in fresh cycles); and prior to embryo transfer. Two experienced sonographers (LTP, MNB) conducted all ultrasound examinations. At least two STIC acquisitions were obtained and examined for presence of artifacts. The dataset with best depiction of endometrial STIC vascularity with no motion or Doppler artifacts was stored and subsequently used in analysis. Machine settings for STIC dataset acquisition were kept constant during all examinations and were: smooth rise/fall 2/2; PRF 0.6 kHz; gain −2; STIC sweep time 15 s; angle of acquisition 90° (max); WMF low 1; balance $>$225; frequency med. All ultrasound images were analyzed offline using 4D View™ software (version 10.5 BT12, GE Medical Systems) by means of manual analysis with and 1 cm^3 spherical sampling. Only images where the VOI was no deeper than 5 cm from the transducer and delineation of the endometrium was possible without doubt were included in order to minimize the effect of attenuation on Doppler signal and provide a reliable endometrial representation, respectively. In brief, the 3D volumes were displayed using the multiplanar view, which demonstrates three sectional planes (the A, B and C planes; see Fig. 1). Plane A displays the sagittal section of the endometrial cavity, plane B – the transverse section and plane C – the coronal reconstruction of the endometrial cavity. The magnification was adjusted to allow for accurate delineation. Volume of the endometrium was measured using virtual organ computer aided analysis (VOCAL), by delineating the endometrial-myometrial junction (EMJ) on the A plane in each of series of static 3DPD volumes comprising the complete STIC acquisition as the volume was rotated through 180° using 15° rotational steps [13]. 3DPD indices (vascularization index – VI, flow index – FI and vascularization flow index – VFI) were obtained using the histogram function from the 4D View™ software available from GE (GE Healthcare Austria GmbH & Co OG) (see Fig. 2). Following manual analysis, spherical sampling using VOCAL software was carried out, so that the edge of the 1 cm^3 sphere was touching the top of the endometrial cavity on plane A and plane C of the multiplanar view (see Fig. 3). Manual and spherical

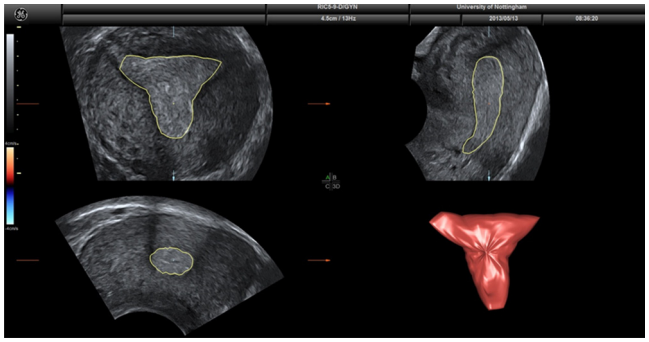

Fig. 1. Multiplanar view. The image demonstrates the multiplanar view of a 3D volume of the endometrium with rendering of the endometrium presented in the bottom right corner of the image.