The role of endometrial and subendometrial vascularity measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during frozen–thawed embryo transfer cycles

Ernest Hung Yu Ng1, Carina Chi Wai Chan, Oi Shan Tang, William Shu Biu Yeung and Pak Chung Ho

Department of Obstetrics and Gynaecology, The University of Hong Kong, Hong Kong SAR, China

1To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, The University of Hong Kong, 6/F, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong SAR, China. E-mail: nghye@hkucc.hku.hk

BACKGROUND: A good blood supply to the endometrium is usually considered as an essential requirement for implantation. OBJECTIVE: The aim of this study was to evaluate the role of endometrial and subendometrial vascularity in the prediction of pregnancy during frozen–thawed embryo transfer (FET) cycles. METHODS: Women undergoing FET in natural or clomiphene-induced cycles after the first stimulated IVF treatment were recruited. A three-dimensional (3D) ultrasound examination with power Doppler was performed 1 day after the LH surge to determine endometrial thickness, endometrial pattern, pulsatility index (PI) and resistance index (RI) of uterine vessels, endometrial volume, vascularization index, flow index and vascularization flow index of endometrial and subendometrial regions. RESULTS: Women in the pregnant group were significantly younger and used less gonadotrophins in their stimulated cycle. Endometrial thickness, endometrial volume, endometrial pattern, uterine PI, uterine RI, endometrial and subendometrial 3D power Doppler flow indices were similar between the nonpregnant and the pregnant groups. The age of women was the only predictive factor for pregnancy. Receiver operating characteristic curve analysis revealed that the area under the curve was around 0.5 for all ultrasound parameters for endometrial receptivity. CONCLUSION: Vascularity of endometrial and subendometrial layers measured by 3D power Doppler ultrasound is not a good predictor of pregnancy in FET cycles if measured at one time point only.

Key words: endometrial and subendometrial vascularity/frozen–thawed embryo transfer/three-dimensional power Doppler

Introduction

Successful implantation depends on a close interaction between the blastocyst and the receptive endometrium. Ultrasound examination of the endometrium allows a noninvasive evaluation of endometrial receptivity (Turnbull et al., 1995). Different ultrasound parameters have been used in IVF treatment, including endometrial thickness, endometrial pattern, endometrial volume, Doppler study of uterine arteries and endometrial blood flow. Endometrial thickness and pattern have low positive predictive value and specificity for the IVF outcome (Turnbull et al., 1995; Friedler et al., 1996), whereas endometrial volume measured by three-dimensional (3D) ultrasound is not predictive of pregnancy (Raga et al., 1999; Yaman et al., 2000; Schild et al., 2001).

Angiogenesis plays a critical role in various female reproductive processes such as development of a dominant follicle, formation of a corpus luteum, growth of endometrium and implantation (Abulafia and Sherer, 2000; Smith, 2001).

A good blood supply towards the endometrium is usually considered as an essential requirement for implantation. Endometrial microvascular blood flow which is determined by an intrauterine laser Doppler technique in the early luteal phase of the cycle preceding an IVF cycle has been shown to be predictive of pregnancy and superior to other conventional parameters predicting endometrial receptivity (Jinno et al., 2001). Uterine blood flow is assumed in many studies to reflect the blood flow towards the endometrium. It is assessed by colour Doppler ultrasound and is usually expressed as downstream impedance to flow because measurement of blood flow volume is difficult and inaccurate, depending on the angle of insonation, accurate measurement of the vessels’ diameter and tortuosity of the vessels (Dickey, 1997). In combination with 3D ultrasound, power Doppler provides a unique noninvasive tool with which to examine the blood supply towards the whole endometrium and the subendometrial region (Schild et al., 2000; Kupesic et al., 2001; Wu et al., 2003; Ng et al., 2004a,b, 2005; Raine-Fenning et al., 2004a).
Significantly higher subendometrial vascularity was shown in pregnant IVF cycles (Kupesic et al., 2001; Wu et al., 2003). However, the vascularity of endometrial and subendometrial layers measured by 3D power Doppler ultrasound was not a good predictor of pregnancy in our recent study (Ng et al., 2006). Its role in the prediction of pregnancy during frozen–thawed transfer (FET) cycles has not been evaluated before. It is possible that the endometrial receptivity in natural cycles is different from that of stimulated cycles. Indeed, we found that endometrial and subendometrial 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., 2004b).

The aim of this prospective study was to compare the endometrial and subendometrial vascularity as measured by 3D power Doppler ultrasound between pregnant and nonpregnant patients during FET cycles. The hypothesis was that the vascularity of the endometrial and subendometrial layer was significantly higher in pregnant patients than that in nonpregnant patients.

Materials and methods

After the first stimulated IVF cycle, infertile patients undergoing FET cycles in the Assisted Reproduction Unit of the Department of Obstetrics and Gynaecology, The University of Hong Kong, between June 2003 and April 2005 were invited to participate in this study. Inclusion criteria were women aged ≤40 years and replacement of at least two frozen–thawed embryos. Patients who had abnormal uterine cavity as shown in the stimulated IVF cycle or required hormonal replacement therapy in FET cycles were excluded. Indications for ICSI treatment included tubal, male, endometriosis, unexplained and mixed factors. ICSI was performed for couples with severe semen abnormalities where <100 000 motile spermatozoa were recovered after sperm preparation. In case of obstructive or nonobstructive azospermia, surgically retrieved spermatozoa from epididymis or testis, respectively, were used for ICSI. Basal serum FSH concentration was checked on days 2 and 3 of the cycle within 2–3 months of commencing the first IVF cycle. Every patient gave her written informed consent before participating in the study, which was approved by the Ethics Committee, Faculty of Medicine, The University of Hong Kong. They were evaluated only once during the study period and did not receive any monetary compensation for their participation in the study.

The details of the long protocol of ovarian stimulation, gamete handling, cryopreservation of embryos and FET were as previously described (Ng et al., 2000). In short, they were pretreated with Buserelin (Suprecur; Hoechst, Frankfurt, Germany) nasal spray 150 μg four times a day from the midluteal phase of the cycle preceding the treatment cycle, and they also received HMG (Pergonal; Serono, Geneva, Switzerland) for ovarian stimulation. HCG (Profasi; Serono, Geneva, Switzerland) was given intramuscularly when the leading follicle reached 18 mm in diameter, and there were at least three follicles of ≥16 mm in diameter. Oocyte retrieval was scheduled 36 h after the HCG injection. Patients were advised to have two embryos replaced into the uterine cavity 48 h after the retrieval, but replacing three embryos was allowed. Excess good-quality embryos were frozen.

Those who did not get pregnant in the stimulated IVF cycle and had ≥2 frozen embryos could undergo FET in natural or clomiphene citrate-induced cycles, at least 2 months after the stimulated cycle. Patients having regular ovulatory cycles would undergo FET in their natural cycles. Clomiphene citrate (Clomid; Merrell, Staines, UK) 50–150 mg was given daily for 5 days from days 3 to 7 to patients with irregular long cycles or absence of serum estradiol (E2) rise and an LH surge in previous natural cycles. They attended the clinic daily from 18 days before the next expected period for the determination of serum E2 and LH concentrations until the LH surge, which was defined as the day on which the LH level was above 20 IU/l and double the average of the LH levels over the previous 3 days. FET was performed on the third day after the LH surge. The luteal phase was supported by two doses of HCG injections. A urine pregnancy test was done 16 days after ET. If it was positive, ultrasound examination was performed 10–14 days later to confirm intrauterine pregnancy and to determine the number of gestational sacs present. Only clinical pregnancies defined by the presence of one or more gestational sacs or the histological confirmation of gestational product in miscarriages were considered.

All ultrasound measurements were performed by E.H.Y.N. on LH+1 using a GE Voluson 730® (GE Kretz, Zürich, Switzerland) at around 8–10 AM after the patient had emptied their bladder. The details of 3D ultrasound and data analysis with the intraobserver reliability were as previously described (Ng et al., 2004a). The results of this ultrasound assessment did not affect subsequent clinical management procedures. The maximum thickness of the endometrium on both sides of the midline was measured in a longitudinal plane. The endometrial pattern visualized was designated as a multilayered or a nonmultilayered endometrium (Sher et al., 1991). A multilayered endometrium presented as a triple-line pattern in which hyperechogenic outer lines and a well-defined central echogenic line were seen with hypoechogenic or black areas between these lines. A nonmultilayered endometrium consisted of homogenous endometrial patterns characterized by either hyperechogenic or isoechogenic endometrium.

Using colour Doppler in the 2D mode, flow velocity waveforms were obtained from the ascending main branch of the uterine artery on the right and left sides of the cervix in a longitudinal plane before they entered the uterus. The gate of the Doppler was positioned when the vessel with good colour signals was identified on the screen. Pulsatility index (PI) and resistance index (RI) of the uterine arteries were calculated electronically when similar consecutive waveforms of good quality were obtained. As there were no differences in uterine PI and RI between the left and the right sides, the averaged uterine PI and RI were given.

The ultrasound machine was switched to the 3D mode with power Doppler. The setting conditions for this study were as follows: frequency, mid; dynamic set, 2; balance, G > 140; smooth, 5/5; ensemble, 12; line density, 7; power Doppler map, 5. Meanwhile, the setting conditions for the subpower Doppler mode were as follows: gain, 6.0; balance, 140; quality, normal; wall motion filter, low 1; velocity range, 0.9 kHz. The resulting truncated sector covering the endometrial cavity in a longitudinal plane of the uterus was adjusted and moved, and the sweep angle was set to 90° to ensure that a complete uterine volume encompassing the entire subendometrium was obtained. The patient and the 3D transvaginal probe remained as still as possible during the volume acquisition. A 3D dataset was then acquired using the medium speed sweep mode. The resulting multiplanar display was examined to ensure that the area of interest was captured in its entirety. If the volume measurement was completed without a power Doppler artefact, the dataset was stored for later analysis by E.H.Y.N.

The built-in Virtual Organ Computer-Aided Analysis (VOCAL®) Imaging Program for the 3D power Doppler histogram analysis was used in the analysis, along with computer algorithms, to measure the endometrial volume and indices of blood flow within the endometrium. Vascularization index (VI), which measures the ratio of...
the number of colour voxels to the number of all the voxels, is thought to represent the presence of blood vessels (vascularity) in the endometrium and is expressed as a percentage of the endometrial volume. Flow index (FI), the mean power Doppler signal intensity inside the endometrium, is thought to express the average intensity of flow. Vascularization flow index (VFI) is a combination of vascularity and flow intensity (Pairleitner et al., 1999). During the analysis and calculation, the manual mode of the VOCAL® Contour Editor was used to cover the whole 3D volume of the endometrium with a 15° rotation step. Hence, 12 contour planes were analysed for the endometrium of each patient to cover 180°. Following the assessment of the endometrium itself, the subendometrium was examined through the application of ‘shell-imaging’, which allows the user to generate a variable contour that parallels the originally defined surface contour. In the present study, the subendometrial region was considered to be within 1 mm of the originally defined myometrial–endometrial contour (Ng et al., 2004a). VI, FI and VFI of the subendometrial region were obtained accordingly.

Serum E₂ and LH concentrations were measured using commercially available kits (Automated Chemiluminescence System; Bay Corporation, NY, USA). The sensitivity of the E₂ assay was 36.7 pmol/l, and the intra- and inter-assay coefficients of variation were 8.1 and 8.7%, respectively. The sensitivity of the LH assay was 0.07 IU/l, and the intra- and inter-assay coefficients of variation were 4.5 and 5.2%, respectively.

**Statistical analysis**

The primary outcome measure was a clinical pregnancy. Continuous variables were not normally distributed and were given as median (interquartile range), unless indicated. Statistical comparison was carried out by Mann–Whitney, chi-square and Fisher’s exact tests, where appropriate. Multiple logistic regression analysis and the receiver operating characteristic (ROC) curve analysis were applied to determine the best predictive variables (Altman and Bland, 1994). Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS, Version 12.0; Chicago, IL, USA). The two-tailed value of $P < 0.05$ was considered statistically significant.

**Results**

A total of 222 women underwent FET during the study period, and only 193 women were recruited into the study because nine women were >40 years old and another 20 women had only one frozen–thawed embryo for transfer. Frozen–thawed embryos were replaced in 164 natural and 29 clomiphene citrate-induced cycles, and 42 (21.8%) clinical pregnancies resulted. There was no significant difference in pregnancy rate between natural (35/164, 21.3%) and clomiphene citrate-induced (7/29, 24.1%) cycles.

Table I compares the demographic data and ovarian responses of the stimulated cycles between the nonpregnant and pregnant groups. Women in the pregnant group were significantly younger and used less HMG in the stimulated cycles, when compared with those in the nonpregnant group. There were no significant differences in the proportion of primary infertility, duration of infertility, cause of infertility, the insemination method, BMI, basal serum FSH concentration, HMG duration and number of oocytes obtained between the nonpregnant and pregnant groups.

No differences were found in the type of FET cycles (Figure 1) and in the number of frozen–thawed embryos replaced between the nonpregnant and pregnant groups. Endometrial thickness, endometrial volume, endometrial pattern, uterine PI, uterine RI, as well as the endometrial and subendometrial 3D power Doppler flow indices were similar between the nonpregnant and pregnant groups (Table II). Endometrial and subendometrial 3D power Doppler flow indices were also comparable for natural and clomiphene citrate-induced cycles (data not shown).

When the age of women, type of infertility, duration of infertility, BMI, number of oocytes obtained, number of frozen–thawed embryos replaced, uterine PI, uterine RI, endometrial thickness, endometrial pattern, endometrial volume and 3D power Doppler flow indices of endometrial and subendometrial regions were entered in a conditional forward fashion in multiple logistic regression analysis, the age of women was the only predictive factor with an odds ratio of 0.893 (95% confidence interval = 0.802–0.995, $P = 0.039$). Other parameters were not predictive of pregnancy. The ROC curve analysis showed that the area under the curve was about 0.5 for the ultrasound parameters for endometrial receptivity (Table III).

**Discussion**

Many studies have been conducted to evaluate the role of various ultrasound parameters in predicting pregnancy during stimulated IVF cycles (Turnbull et al., 1995; Friedler et al., 1996; Dickey, 1997), but little information exists in the literature with regard to their role in FET cycles (Ueno et al., 1991; Al-Shawaf et al., 1993; Coulam et al., 1994; Cacciapere and Tiitten, 1996; Basir et al., 2002). To the best of our knowledge, this is the first study addressing the role of the endometrial and subendometrial vascularity measured by 3D power Doppler ultrasound in the prediction of pregnancy during FET.

Table I. Comparison of demographic data and ovarian responses of the stimulated cycle between nonpregnant and pregnant patients

<table>
<thead>
<tr>
<th></th>
<th>Nonpregnant ($n = 151$)</th>
<th>Pregnant ($n = 42$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of women (years)</td>
<td>35.0 (32.0–37.0)</td>
<td>33.0 (31.0–35.0)</td>
<td>0.030*</td>
</tr>
<tr>
<td>Primary infertility [%]</td>
<td>85 (56.3)</td>
<td>23 (54.8)</td>
<td>0.860</td>
</tr>
<tr>
<td>Infertility duration (years)</td>
<td>4.0 (3.0–6.0)</td>
<td>5.5 (3.8–8.0)</td>
<td>0.056</td>
</tr>
<tr>
<td>Causes of infertility [%]</td>
<td></td>
<td></td>
<td>0.798</td>
</tr>
<tr>
<td>Tubal</td>
<td>32 (21.2)</td>
<td>11 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85 (56.3)</td>
<td>22 (52.4)</td>
<td></td>
</tr>
<tr>
<td>Endometrosis</td>
<td>15 (9.9)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>9 (6.0)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>10 (6.6)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Insemination method [%]</td>
<td></td>
<td></td>
<td>0.808</td>
</tr>
<tr>
<td>Conventional</td>
<td>94 (62.3)</td>
<td>25 (59.5)</td>
<td></td>
</tr>
<tr>
<td>ICSI</td>
<td>57 (37.7)</td>
<td>17 (40.5)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.4 (19.9–22.9)</td>
<td>21.2 (20.1–23.7)</td>
<td>0.751</td>
</tr>
<tr>
<td>Basal FSH concentration (IU/l)</td>
<td>5.9 (4.8–7.0)</td>
<td>5.9 (4.8–6.9)</td>
<td>0.740</td>
</tr>
<tr>
<td>HMG dosage (IU)</td>
<td>1800 (1650–2100)</td>
<td>1728 (1556–1950)</td>
<td>0.014*</td>
</tr>
<tr>
<td>HMG duration (days)</td>
<td>11.0 (9.0–12.0)</td>
<td>10.0 (9.0–11.0)</td>
<td>0.114</td>
</tr>
<tr>
<td>Number of oocytes obtained</td>
<td>12.0 (9.0–17.0)</td>
<td>13.0 (8.0–19.3)</td>
<td>0.648</td>
</tr>
</tbody>
</table>

Data given as median (interquartile range).

*Statistically significant.
cycles. Our patients received a standard long protocol of pituitary down-regulation in their first IVF cycle. Excess embryos were all frozen 2 days after the oocyte retrieval, and frozen embryos were thawed and replaced 3 days after the LH surge in natural or clomiphene citrate-induced cycles. All patients were scanned early in the morning, 1 day after the LH surge. Those women aged >40 or having only one frozen embryo were excluded because they had a much lower pregnancy rate (Karlstrom et al., 1997; Wang et al., 2001).

In the present study, we found that endometrial thickness, endometrial volume, endometrial pattern, uterine PI, uterine RI, and endometrial and subendometrial 3D power Doppler flow...
Comparison of ultrasound parameter for endometrial receptivity between the nonpregnant and pregnant patients

Receiver operating characteristic (ROC) curve analysis of endometrial volume (cm³) 4.34 (3.32–5.60) 4.68 (3.31–6.06) 0.411
Endometrial thickness (mm) 10.9 (9.7–13.1) 11.4 (9.5–13.2) 0.503

Table II. Comparison of ultrasound parameter for endometrial receptivity between the nonpregnant and pregnant patients

<table>
<thead>
<tr>
<th>Test variables</th>
<th>Nonpregnant (n = 151)</th>
<th>Pregnant (n = 42)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial thickness (mm)</td>
<td>10.9 (9.7–13.1)</td>
<td>11.4 (9.5–13.2)</td>
<td>0.503</td>
</tr>
<tr>
<td>Endometrial volume (cm³)</td>
<td>4.34 (3.32–5.60)</td>
<td>4.68 (3.31–6.06)</td>
<td>0.411</td>
</tr>
<tr>
<td>Endometrial pattern [%]</td>
<td></td>
<td></td>
<td>0.911</td>
</tr>
<tr>
<td>Multilayered</td>
<td>149 (98.7)</td>
<td>42 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Nonmultilayered</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Uterine pulsatility index</td>
<td>2.00 (1.73–2.34)</td>
<td>1.97 (1.68–2.46)</td>
<td>0.911</td>
</tr>
<tr>
<td>Uterine resistance index</td>
<td>0.83 (0.78–0.87)</td>
<td>0.83 (0.78–0.87)</td>
<td>0.821</td>
</tr>
<tr>
<td>Endometrial vascularization index (VI) [%]</td>
<td>1.669 (0.558–3.647)</td>
<td>1.447 (0.558–3.435)</td>
<td>0.760</td>
</tr>
<tr>
<td>Endometrial flow index (FI) (0–100)</td>
<td>23.970 (22.052–26.351)</td>
<td>24.020 (22.235–26.348)</td>
<td>0.754</td>
</tr>
<tr>
<td>Endometrial vascularization flow index (VFI) (0–100)</td>
<td>0.425 (0.125–0.972)</td>
<td>0.330 (0.124–0.914)</td>
<td>0.801</td>
</tr>
<tr>
<td>Subendometrial VI [%]</td>
<td>3.407 (1.367–8.365)</td>
<td>3.043 (1.447–8.733)</td>
<td>0.933</td>
</tr>
<tr>
<td>Subendometrial FI (0–100)</td>
<td>25.043 (23.007–27.305)</td>
<td>24.661 (22.090–26.980)</td>
<td>0.399</td>
</tr>
<tr>
<td>Subendometrial VFI (0–100)</td>
<td>0.910 (0.294–2.064)</td>
<td>0.756 (0.222–2.310)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Data given as median (interquartile range) except for endometrial pattern.

In contrast, we recently reported in a much larger study that endometrial VI and VFI measured on the day of oocyte retrieval were significantly lower in the pregnant group than in the nonpregnant group (Ng et al., 2006). In that study, ROC curve analysis also revealed that the area under the curve was around 0.5 for all ultrasound parameters for endometrial receptivity. Results of the present study supported the findings of our previous study (Ng et al., 2006). It appears that the vascularity of endometrial and subendometrial layers measured by 3D power Doppler ultrasound was not a good predictor of pregnancy during stimulated IVF and FET cycles if it was measured at one time point only.

Our results are not contradictory to those studies that specifically examined perfusion within the human endometrium during the menstrual cycle. Fraser et al. (1987) determined endometrial blood flow through the menstrual cycle with the use of the clearance of radiolabelled xenon-133 following its instillation into the uterine cavity. There was a significant elevation in the middle-to-late follicular phase, followed by a substantial fall and a secondary slow luteal phase rise that was maintained until the onset of menstruation. More recently, Raine-Fenning et al. (2004a) showed that endometrial and subendometrial vascularity by 3D ultrasound increased during the proliferative phase, peaking around 3 days prior to ovulation before decreasing to a nadir 5 days post-ovulation.

Raine-Fenning et al. (2004b) further proposed that the degree of change in endometrial perfusion from the late follicular phase through to the early luteal phase was a more important determinant of endometrial receptivity. Hypoxia in the endometrium may play a beneficial role for implantation as the expression of vascular endothelial growth factor is up-regulated by hypoxia (Sharkey et al., 2000), and relatively low oxygen tension was present around the blastocyst during the time of implantation (Graham et al., 2000). To confirm or refute this hypothesis, further longitudinal studies on the endometrial and subendometrial vascularity should be performed in the late follicular and early luteal phases.

There were no differences in pregnancy rate and 3D power Doppler flow indices of endometrial and subendometrial regions between natural and clomiphene citrate-induced cycles, although clomiphene citrate may exert its anti-estrogenic action.
on the endometrium, leading to reduced endometrial thickness (Nakamura et al., 1997) and delayed endometrial maturation (Massai et al., 1993). However, a randomized study would be required to show any differences in 3D power Doppler flow indices of endometrial and subendometrial regions between natural and clomiphene citrate-induced cycles.

In conclusion, the vascularity of endometrial and subendometrial layers measured by 3D power Doppler ultrasound was not a good predictor of pregnancy during FET cycles if they were measured at one time point only.

Acknowledgements
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