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ARTICLE

Assessment of endometrial and subendometrial blood flow in women undergoing frozen embryo transfer cycles

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Abstract This study evaluated whether 3D power Doppler (3DPD) indices from endometrium and subendometrium can identify increases in endometrial volume/vascularity induced by exogenous oestradiol and subsequent introduction of progestogens in women undergoing frozen–thawed embryo transfer (FET). Oral oestradiol was administered at increasing doses after down-regulation to prepare the endometrium and progestogens were used for luteal support. 3DPD data sets were acquired at down-regulation, on days 5, 10 and 15 of oestradiol administration and at the time of FET. Endometrial thickness was measured using the multiplanar method and endometrial volume and blood flow from the endometrium and subendometrium were estimated using virtual organ computer-aided analysis and shell-imaging. This study evaluated 45 women at least once: 19 achieved clinical pregnancy (CP); 21 were evaluated at down-regulation (eight CP), 26 at day 5 (10 CP), 31 at day 10 (12 CP), 31 at day 15 (13 CP) and 16 at FET (seven CP). Changes were observed in all parameters between the examinations; however, differences between women who achieved CP and those who did not were not significant. 3DPD angiography is not a sufficiently sensitive tool to predict the outcome of FET.

KEYWORDS: endometrial vascularity, frozen embryo transfer, frozen embryo replacement, three-dimensional power Doppler, sub endometrial blood flow, frozen-thawed embryo transfer

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Introduction

A good blood supply to the endometrium and subendometrium is essential for successful implantation (Jinno et al., 2001; Wang et al., 2010). Although endometrial development throughout the menstrual cycle and during assisted reproduction treatment has been well described (Jokubkiene et al., 2006; Raine-Fenning et al., 2004b), the relationship of blood flow assessed by ultrasonography with implantation remains unclear (Raine-Fenning, 2008). Several groups have used Doppler to assess blood flow within the endometrium and subendometrium (Chien et al., 2002; Nakai et al., 2002; Yang et al., 1999; Zaidi et al., 1995) but it is difficult to obtain an accurate and reliable measurement of blood flow because of the low flow rates and tortuous nature of the spiral arteries (Friedler et al., 1996; Hsieh et al., 2000; Nelson and Pretorius, 1988; Pierson, 2003; Vieli, 1990). Three-dimensional ultrasound in combination with power Doppler ultrasound (3DPD) is able to analyse the whole vascular tree (Ng et al., 2005; Raine-Fenning, 2004; Raine-Fenning et al., 2004c; Schild et al., 2000; Wu et al., 2003) and also permits the quantification of power Doppler signals by using three indices: vascularization index, flow index and vascularization flow index (Raine-Fenning, 2004; Riccabona et al., 1996; Rizzatto, 2001).

3DPD angiography has been used to examine the changes in endometrial and subendometrial blood flow during IVF treatment and evaluate their relationship to subsequent pregnancy (Merce et al., 2008; Ng et al., 2006d; Schild et al., 1999; Wu et al., 2003). The majority of the studies have, however, limited their assessment to a single time point, such as final follicular maturation (Ng et al., 2005, 2006d; Wu et al., 2003), the day of oocyte retrieval (Ng et al., 2006a,b,c) or the day of embryo transfer (Ng et al., 2009). As endometrial and subendometrial blood flow have been shown to change with time and to be influenced by the serum concentrations of sex steroids (Raine-Fenning et al., 2004b), this one-stop approach is not predictive of pregnancy in frozen–thawed embryo transfer (FET) cycles (Ng et al., 2006a,d).

Serial assessment of blood flow assesses cyclical change but to date there is limited information on this. As far as is known, only one study has been carried out using two time points and this was conducted in patients undergoing a fresh cycle of IVF with concomitant ovarian stimulation that itself is known to influence pelvic blood flow (Ng et al., 2009). FET, where the endometrium is artificially prepared with hormones, provides a model to assess these serial changes.

This study was primarily designed to evaluate whether 3DPD indices, such as endometrial thickness and volume, vascularization index, vascularization flow index and flow index (flow index) from endometrium and subendometrium, can identify the expected changes in endometrial development and blood flow and comparing these values between women who achieved clinical pregnancy (CP) and those who did not.

Materials and methods

Study design

This was a prospective, longitudinal observational (cohort) study, done as pilot to look at the ability of 3DPD to detect predicted changes in endometrial thickness, volume and blood flow.

Participants and setting

Subfertile women attending Nottingham University's Research and Treatment Unit in Reproduction (NURTURE) between January 2007 and December 2007 for FET were assessed. Inclusion criteria were women undergoing FET after their first stimulated IVF treatment who had a normal uterus on ultrasound without evidence of any myometrial or endometrial pathology or uterine abnormality. None of them had a pregnancy from their stimulated IVF treatment. Only women requiring hormonal replacement therapy in FET cycles were included (women undergoing FET in natural cycles were not included). Each woman had two frozen–thawed embryos transferred during the treatment. Ethical approval was not required as the study followed standard departmental clinical practice and no additional visits or procedures were imposed on the patients. This decision was made after discussion with the research and development department of the Trust. All participants signed informed consent.

The endometrial preparation was performed as follows: gonadotrophin-releasing hormone (GnRH) agonist was used, prior to the administration of oestrogen, to induce pituitary desensitization and suppression of ovarian function and prevent an unscheduled and premature rise in LH. A standard regime of GnRH agonist (buserelin; Suprecur; Sanofi-Aventis, Guildford, UK) was administered subcutaneously at a daily dose of 0.5 ml or as a 300 μg nasal spray taken three times daily from the mid-luteal phase of the menstrual cycle prior to the actual FET cycle. The first visit was scheduled for 14 days after the commencement of GnRH agonist to confirm pituitary suppression through the demonstration of reduced ovarian activity as manifest by a thin endometrium (thickness $\leq$5 mm). If these criteria were met and the patient had menstruated, successful down-regulation was considered to have occurred. Once down-regulation was confirmed, oral oestradiol valerate (Progynova; Bayer; Newbury, UK) was commenced at a dose of 2 mg once daily. The dose was increased 5 days later (day 5) to 4 mg daily (given as 2 mg twice daily) and then to 6 mg daily (given as 2 mg three times per day) after a further 5 days (day 10). On day 15 of oestradiol valerate administration, progestogen vaginal pessaries (Cyclogest 400 mg twice daily; Actavis, UK) were started in addition to the oral oestrogen, and embryo transfer conducted 4 days later (final visit) in accordance with the unit's standard operating protocol.

Data measurement

Ultrasound scans were scheduled at each visit: down-regulation, day 5, day 10, day 15 and FET. The ultrasound examinations were conducted by one observer (JSC) with a Voluson E8 Expert (GE Medical Systems) ultrasound machine. Each patient was scanned in a supine position with knees flexed and hips abducted. The pelvis was first assessed to identify/rule out any abnormality within the uterus or ovaries. The uterus was then located and power