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Assessment of endometrial volume by three-dimensional ultrasound prior to embryo transfer: clues to endometrial receptivity

F.Raga[1,2,4], F.Bonilla-Musoles[1,2], E.M.Casañ[1,2], O.Klein[2,3] and F.Bonilla[1,2]

[1]Center for Obstetrics and Gynecology, [2]Department of Obstetrics and Gynecology, University of Valencia School of Medicine, Valencia, Spain and [3]Department of Genetics, Yale University School of Medicine, Connecticut, USA

[4]To whom correspondence should be addressed at: Center for Obstetrics and Gynecology, Pedro Aleixandre 57–7, 46006-Valencia, Spain

The aim of the present prospective study was to obtain quantitative data on endometrial volume by three-dimensional (3D) ultrasound at the time of embryo transfer in an in-vitro fertilization programme and to assess its value in predicting endometrial receptivity. The cycles ($n = 72$) were classified according to endometrial volume: group A <2 ml, group B 2–4 ml, and group C >4 ml. Comparisons of the groups showed that pregnancy and implantation rates were significantly lower ($P < 0.05$) in the group of patients with an endometrial volume <2 ml. Furthermore, no pregnancy was achieved with an endometrial volume <1 ml. It is concluded that endometrial volume by 3D transvaginal ultrasound may become a new objective parameter by which to predict endometrial receptivity.

Key words: assisted conception/endometrial volume/reproductive performance/three-dimensional ultrasound

Introduction

Since the introduction of assisted conception, many techniques have been developed to improve ovarian stimulation, oocyte retrieval, in-vitro fertilization (IVF) and embryo culture, but despite this, more than 70% of apparently normal embryos transferred on day 2 fail to implant (Turnbull *et al.*, 1995; Tazuke and Giudice, 1996).

The term 'uterine receptivity' refers to a state when endometrium allows a blastocyst to attach, penetrate and induce changes in the stroma which result in embryonic implantation. Although the physiological and biochemical determinants which allow endometrium to enter into the state of receptivity for human embryo attachment and implantation remain poorly understood (Ghosh and Sengupta, 1998; Casañ *et al.*, 1999), various endocrine parameters correlated with endometrial receptivity and implantation are well documented (Ghosh and Sengupta, 1998; Raga *et al.*, 1998, 1999a).

Endometrial differentiation, embryo development, and embryo-endometrial interactions leading to implantation require continuous and synchronous dialogue between these two compartments. Since the introduction of transvaginal sonography, a number of studies have attempted to define a relationship between endometrial thickness, echogenicity and endometrial receptivity. Unfortunately, the sonographic parameters used to predict uterine receptivity still lack specificity, and so the ideal method to predict endometrial receptivity by a non-invasive method has yet to be established. With the advent and evolution of three-dimensional (3D) ultrasound we now stand at a new threshold in non-invasive diagnosis.

The standard method of endometrial dating is the histological evaluation of an endometrial biopsy specimen (Noyes *et al.*, 1950). Indeed, this technique has allowed the demonstration of asynchrony in endometrial development during the course of cycles of ovarian stimulation for IVF leading to cancellation of embryo transfer (Frydman *et al.*, 1982; Cohen *et al.*, 1984; Sterzik *et al.*, 1997). Obviously, the invasiveness of endometrial biopsy is not acceptable in the clinical context of assisted reproduction treatment cycles.

As endometrial biopsy is invasive and assessment of the hormonal milieu inadequate, the need to evaluate endometrial development encouraged the use of high-resolution ultrasonography as an alternative, non-invasive method of assessment of endometrial receptivity (Shoham *et al.*, 1991; Friedler *et al.*, 1996). Two anatomical parameters have been used to evaluate endometrial receptivity by ultrasound: endometrial thickness and endometrial pattern. Unfortunately, these sonographic parameters lack specificity (Friedler *et al.*, 1996; Gentry *et al.*, 1996; Remohi *et al.*, 1997; Sundström, 1998). Therefore, the ideal method to predict endometrial receptivity has yet to be established.

Current advances in transvaginal 3D ultrasonography have allowed us to examine in detail and visualize pelvic organ structures, and to analyse their volumes with great accuracy (Steiner *et al.*, 1994; Bonilla-Musoles, *et al.*, 1995a,b; Raga *et al.*, 1996; Blaas *et al.*, 1998). Moreover, the ability to reconstruct 3D plastic images amplifies the diagnostic potential of two-dimensional (2D) ultrasound and enables us to conduct meticulous investigations of the uterine cavity (Jurkovic *et al.*, 1995, 1997; Raga *et al.*, 1996; Wu *et al.*, 1997).

Furthermore, recent studies have demonstrated the high degree of reproducibility and accuracy of volume estimation using 3D ultrasound both *in vitro* and *in vivo* (Gilja *et al.*, 1994; Bonilla-Musoles *et al.*, 1995c; Lee *et al.*, 1996; Blaas *et al.*, 1998). Volume estimation of the endometrium can be made easily because of good contrast between endometrial tissue and myometrium by 3D transvaginal ultrasound (Gruboeck *et al.*, 1996; Kyei-Mensah *et al.*, 1996; Lee *et al.*, 1997).

The ability to identify a receptive uterus prospectively by a non-invasive method would have an invaluable impact on

treatment efficiency and success rates following assisted reproduction. Therefore, the aim of the present study was to obtain quantitative data on endometrial volume at the time of embryo transfer in IVF patients and to assess its value in the prediction of endometrial receptivity.

Materials and methods

Patients

We prospectively studied 72 consecutive ovarian stimulation cycles undertaken in 72 candidates for IVF–embryo transfer due to sperm abnormalities (35%), tubal pathology (22%), unexplained infertility (14%) and endometriosis (29%). All patients had normal ovulatory cycles and good physical and mental health. Only women aged <38 years undergoing their first IVF cycle, whose uteri were morphologically normal as confirmed by 3D ultrasound and hysterosonography (Raga *et al.*, 1996; Bonilla-Musoles *et al.*, 1997), and who had at least three good quality embryos (i.e. <20% embryo fragmentation) (Ubaldi *et al.*, 1996) available for embryo transfer were selected.

The local ethics committee approved the study protocol, and written informed consent was obtained from all patients.

Study design

The objective of the present study was to assess the value of endometrial volume determined by 3D transvaginal ultrasound as a predictor of endometrial receptivity in IVF–embryo transfer patients. No attempt was made to compare endometrial thickness by 2D ultrasound with endometrial volume by 3D ultrasound.

The ovarian stimulation protocol began with the administration of 300 IU/day of recombinant human follicle stimulating hormone (rFSH) (two vials of 150 IU rFSH, Puregon; Organon, Barcelona, Spain) for the first 4 days. Afterward, the dose was adjusted according to follicular development as assessed by transvaginal ultrasound scanning and serum oestradiol concentrations (Raga *et al.*, 1999b). The criteria for human chorionic gonadotrophin (HCG) administration (10 000 IU Profasi®; Serono, Madrid, Spain) were the presence of at least two follicles ⩾18 mm at greatest diameter, and serum oestradiol concentrations >800 pg/ml. rFSH injections were discontinued on the day of HCG administration. Oocyte retrieval 36–38 h after HCG administration, fertilization procedures, and embryo transfer were done according to local methods (Raga *et al.*, 1999b; both procedures were performed by the same author, F.B.-M.). Micronized vaginal progesterone (Progeffik®; Effik laboratories, Madrid, Spain) pills (400 mg/day) were prescribed for luteal support, starting on the evening of the day of embryo transfer.

On the day of embryo transfer (48 h after oocyte retrieval), the women were scanned by 3D ultrasound using a transvaginal 7.5 MHz transducer (Combison 530; Kretztechnik AG, Zipf, Austria) by a single operator (F.R.). Once the uterus was identified and centred in a longitudinal section, a volume box was superimposed on the scan image. The volume was captured through the automatic sweep of the transducer over the region selected. As a result, three orthogonal planes of the uterus were displayed simultaneously on the screen. Rotation and translation of the sonographic planes provided exact frontal, sagittal and horizontal sections through the uterine cavity. The volume of the endometrium was measured by outlining the areas of multiple parallel sections (at least 12 serial slices) and calculated using the trapezoid formula, as previously described (Bonilla-Musoles *et al.*, 1995c; Wu *et al.*, 1998). In addition, the entire uterine volume was also calculated as previously reported (Lee *et al.*, 1997).

Table I. Clinical data for patients grouped according to endometrial volume on the day of embryo transfer

	Groups		
	A (<2 ml)	B (2–4 ml)	C (>4 ml)
Cycles	20	28	24
Indication (%)			
Sperm abnormalities	7 (35)	10 (35.8)	8 (33.5)
Tubal pathology	4 (20)	5 (17.7)	6 (25)
Unexplained 3 (15)	5 (17.9)	3 (12.5)	
Endometriosis	6 (30)	8 (28.6)	7 (29)
Age (years)[a]	34 ± 0.7	33 ± 0.5	31 ± 0.8
BMI (kg/m^2)[a]	22.55 ± 2.43	23.76 ± 2.05	23.12 ± 3.06
Treatment length (days)[a]	9.4 ± 0.22	9.1 ± 0.43	8.9 ± 0.34
Total rFSH dose (IU)[a]	2700 ± 300	2550 ± 300	2850 ± 300
Oocytes retrieved[a]	10 ± 2.2	13 ± 1.5	11 ± 2.6
No. embryos transferred[a]	3.4 ± 0.5	3.2 ± 0.3	3.5 ± 0.6
Implantation rate (%)	4/68 (6)*	13/90 (14)	13/84 (15)
No. of pregnancies (% per cycle)	3 (15)*	9 (32)	9 (37)

[a]Values are means ± SD.
*Significantly different groups ($P < 0.05$)
BMI = body mass index; rFSH = recombinant follicle stimulating hormone.

Statistical analysis

Data are expressed as mean ± SEM. For statistical comparison between groups, χ^2-test and analysis of variance (ANOVA) were applied. Bonferroni's and Scheffé's tests were applied when ANOVA showed statistically significant differences. $P < 0.05$ was considered statistically significant. The analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA).

Results

Clear morphology of the endometrium was obtained in all 72 patients using 3D transvaginal ultrasound at the time of embryo transfer. The duration of patient examination was ~5 min. The volumetric data were stored on a 540 MB rewritable optical disk (Sony, Madrid, Spain). At this point, the examination of the patient was complete. Afterwards, volume calculation took an average of 4 min.

The mean age (± SD) of the study group was 33 ± 4.02 years and mean duration of infertility 4.2 years. Table I shows the demographic characteristics and IVF parameters in the study group.

The mean endometrial volume (± SD) was 2.82 ± 0.85 ml (range 0.18–6.1 ml). In addition, the entire uterine volume was obtained, revealing a mean volume of 46 ± 7.45 ml (range 39.6–51.2 cm^3). No specific measurements of uterine height or width were made; however, they appeared to be similar in all the patients included in the study.

Women were divided into three groups depending on the endometrial volume data (Table I): groups A, B and C with endometrial volume <2, 2–4 and >4 ml respectively. No differences in terms of age, body mass index, uterine volume (data not shown), and reason for IVF–embryo transfer were found between these groups. Furthermore the number of days of ovarian stimulation, total rFSH dose administered, number of oocytes retrieved, and number of good quality (i.e <20%

embryo fragmentation) (Ubaldi *et al.*, 1996) were comparable between groups.

However, the pregnancy and implantation rates showed significant differences between groups (Table I). Patients with an endometrial volume <2 ml (group A) had significantly ($P < 0.05$) lower pregnancy and implantation rates as compared with the groups of women with 2–4 ml (group B) and >4 ml (group C). Moreover, no differences were observed between the latter two groups (group B and C).

On the other hand, the minimum endometrial volume associated with pregnancy was 1.2 ml, and therefore no conception was achieved when the endometrial volume was <1 ml.

Discussion

The results showed that 3D transvaginal ultrasound enables measurement of endometrial volume in all patients undergoing ovulation induction for IVF–embryo transfer. This is in agreement with previous studies demonstrating that the endometrium shows good contrast with the myometrium by 3D transvaginal ultrasound and therefore, measurements of endometrial growth can be performed easily (Gruboeck *et al.*, 1996; Kyei-Mensah *et al.*, 1996; Lee *et al.*, 1997; Rempen, 1998; Schild *et al.*, 1999). Moreover, studies with magnetic resonance imaging or computed tomography have previously demonstrated similar results in endometrial volume estimation (Turnbull *et al*, 1994; Lee *et al*, 1997) but unfortunately these methods are costly and still in their infancy in reproductive medicine.

Endometrial thickness is an ultrasonographic parameter that is easily measurable by 2D transvaginal ultrasonography, and represents endometrial growth during the menstrual cycle (Turnbull *et al.*, 1995; Friedler *et al.*, 1996). There has been considerable controversy concerning the value of endometrial thickness in the prediction of endometrial receptivity. Several groups report a significantly higher mean endometrial thickness measurement in conception compared with non-conception cycles (Turnbull *et al.*, 1995; Friedler *et al.*, 1996). Furthermore, it has become widely accepted that a minimum endometrial thickness (6 mm) is necessary to achieve a pregnancy (Friedler *et al.*, 1996).

However, recent evidence indicates that embryonic implantation is possible even when endometrial thickness is <4 mm (Remohi *et al.*, 1997; Sundström, 1998). Moreover, cycles with endometrial thickness <6 mm yielded implantation and pregnancy rates comparable with those of endometrial thickness 7–9, 9–11 and >12 mm at the time of oocyte donation (Remohi *et al.*, 1997).

Synchronized development of embryo and endometrium is a prerequisite for blastocyst implantation. This is dependent upon the actions of oestrogen and progesterone, and therefore adequate cell proliferation and differentiation during the proliferative phase must be followed by timely changes during the luteal phase with stromal decidualization (Tazuke and Giudice, 1996; Ghosh and Sengupta, 1998). However, several authors have noted no correlation between serum oestradiol concentrations, endometrial thickness and endometrial receptivity (Turnbull *et al.*, 1995; Friedler *et al.*, 1996; Remohi *et al.*, 1997).

Endometrial thickness by 2D transvaginal ultrasound does not include total volume of the endometrium and therefore provides limited information on endometrial growth and differentiation (Friedler *et al.*, 1996). Furthermore, 3D information is essential for accurate volume calculation (Bonilla-Musoles *et al.*, 1995c; Hösli *et al.*, 1998) and can be easily gained by 3D ultrasound (Gilja *et al.*, 1994; Lee *et al.*, 1996; Schild *et al.*, 1999). This information has considerable value in the study of both normal and pathological endometrium (Bonilla-Musoles *et al.*, 1995b; Gruboeck *et al.*, 1996; Kyei-Mensah *et al.*, 1996; Raga *et al.*, 1996; Lee *et al.*, 1997; Schild *et al.*, 1999).

The ability to quantify accurately the endometrial volume using 3D transvaginal ultrasound may help us to predict endometrial receptivity, because cycle outcome can be related to a quantitative parameter rather than endometrial thickness, which is prone to greater subjective variations in measurement. We have shown that endometrial volume is related to pregnancy and implantation rate. It seems that an endometrial volume >2 ml is a prerequisite for good endometrial receptivity. Moreover, no pregnancy was achieved when endometrial volume was <1 ml. On the other hand, once an endometrial volume of >2 ml was reached, no relationship was apparent in terms of endometrial receptivity increasing if endometrial volume increased from 2–4 ml to >4 ml. This is in agreement with a recent report showing no relationship between mean endometrial volume measured by 3D ultrasound and IVF outcome (Schild *et al.*, 1999). Therefore it is conceivable that once this minimum endometrial growth is reached, paracrine/autocrine factors may play a substantial role in embryo/endometrial interactions during early implantation.

In conclusion, the present study was undertaken to evaluate the role of endometrial volume, determined by 3D transvaginal ultrasound, as a predictor of uterine receptivity following embryo transfer in IVF patients. Our data suggest that 3D vaginal sonography is an accurate measurement of endometrial receptivity. In addition, vaginal 3D ultraound is non-invasive, relatively inexpensive, and, most importantly, can provide information during the cycle of interest about whether to perform embryo transfer or to cryopreserve the embryos until endometrium is receptive during a future cycle.

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