Human Reproduction vol.12 no.1 pp.45–50, 1997

The embryo versus endometrium controversy revisited as it relates to predicting pregnancy outcome in in-vitro fertilization–embryo transfer cycles

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To evaluate embryonic and endometrial factors for their value in predicting pregnancy outcome in in-vitro fertilization (IVF) and embryo transfer, a retrospective data collection and prospective uterine artery colour Doppler imaging study was performed in a university-based IVF–embryo transfer programme setting. A total of 210 patients were included and grouped as follows: (I) IVF with controlled ovarian stimulation (214 cycles); (II) frozen–thaw cycle of autologous embryos (30 cycles); (III) oocyte donation, no cryopreservation (12 cycles); (IV) frozen–thaw cycle with embryos from donated oocytes (10 cycles). Embryo quality was significantly better in pregnant than non-pregnant cycles (group I, $P = 0.0104$; groups II–IV, $P = 0.0418$). The endometrial echo was significantly thicker in pregnant versus non-pregnant patients in group I ($P = 0.0059$), but not in groups II–IV ($P = 0.741$). Past uterine surgery or abnormalities had no effect on pregnancy outcome. There were no significant differences in mean uterine artery resistance index or peak systolic velocity in pregnant versus non-pregnant patients in groups II–IV. Thus, embryo quality is the most reliable predictor of pregnancy outcome. Endometrial measurements were significantly thicker in subsequently pregnant patients only in group I, where the endometrium reflects the hormonal environment. Doppler parameters were not useful in predicting pregnancy outcome.

Key words: colour Doppler imaging/embryo transfer/embryo quality/endometrial thickness/in-vitro fertilization/uterine surgery or abnormality

Introduction

Despite improvements both in ovarian stimulation regimens and in fertilization rates in in-vitro fertilization (IVF)–embryo transfer cycles (Society for Assisted Reproductive Technology, 1995), the pregnancy rate has failed to increase correspondingly. The limiting factor seems to be failure of implantation. The quality of the embryos transferred, catheter type and endometrial condition may contribute to the success of implantation and pregnancy outcome following embryo transfer. Past studies have focused on the importance of embryo quality versus uterine receptivity in successful implantation and have resulted in conflicting conclusions (Fleischer *et al.*, 1986; Rabinowitz *et al.*, 1986; Gonen *et al.*, 1989; deZiegler and Frydman, 1990; Check *et al.*, 1993; Shapiro *et al.*, 1993; Check, 1994; Coulam *et al.*, 1994; Giorgetti *et al.*, 1995; Noyes *et al.*, 1995). Although ovarian stimulation and assessment of embryo quality have developed in a standardized way, reliable parameters for predicting uterine receptivity are still sorely needed. Unfortunately, neither endometrial thickness and pattern nor Doppler evaluation of uterine perfusion have been consistently predictive of pregnancy outcome.

We re-examined these parameters to determine which factors, if any, involved in embryo transfer have a predictive value for successful implantation and pregnancy. In analysing the receptivity of the uterus, we used transvaginal ultrasound (TVUS) to visualize the endometrium and to measure blood flow through the uterine arteries.

Materials and methods

Data from patients in four protocol groups were analysed retrospectively. Group I underwent 214 IVF cycles with oocyte aspiration and subsequent embryo transfer. Patients with a thaw cycle of their own cryopreserved embryos were classified as group II (30 cycles). Recipients of donated oocytes in a fresh cycle comprised group III (12 cycles), while those recipients receiving frozen–thawed donated embryos comprised group IV (10 cycles). Uterine artery Doppler flow data was prospectively collected for groups II–IV.

Group I protocol

Patients were given a Metrodin (Serono Laboratories, Norwell, MA, USA) and human menopausal gonadotrophin (Pergonal; Serono Laboratories) regimen following down-regulation with leuprolide acetate (Lupron; TAP Pharmaceutics, North Chicago, IL, USA) or, occasionally, nafarelin acetate (Synarel; Syntex, Palo Alto, CA, USA) started during the luteal phase on day 21. The drug regimen continued for 6–17 days, depending on individual patient response. When there were at least two follicles $>$16 mm in mean diameter with corresponding oestradiol concentrations of ~200–300 pg/ml per mature follicle, human chorionic gonadotrophin (HCG, 10 000 IU i.m.) was administered. Oocyte retrieval followed in 2 days, and, if fertilization occurred, embryo transfer was performed 2 days later.

Groups II–IV

In groups II–IV the uterus was prepared with daily oral oestradiol (Estrace, Bristol-Myers Squibb Co, Princeton, NJ, USA) ranging in dose from 2 to 12 mg or, occasionally, with a 100–400 mg Estraderm patch (Estraderm Transderman System; Ciba Pharmaceutical Co, Summit, NJ, USA). With a goal of $\geqslant$8 mm endometrial thickness, participants were treated for 2–6 weeks to achieve the thickest possible endometrium. For patients with spontaneous menses, suppression after

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gonadotrophin-releasing hormone (GnRH) agonist (Lupron) down-regulation was documented by ultrasound and oestradiol concentrations prior to initiating oestrogen. TVUS for endometrial thickness and pattern and uterine artery colour Doppler imaging studies were performed on day 13 of this treatment regimen. Daily progesterone, 50 mg i.m., was started 4 days before the embryo transfer, and both hormonal treatments were continued during the luteal phase. For oocyte donation, the 100 mg i.m. dose of progesterone was administered.

Endometrial measurements

Endometrial thickness was measured using TVUS (Siemens 450 or Quantum Color Doppler 2000, 5 MHZ endovaginal probe; Siemens Laboratories, Washington DC, USA), using a 'frozen' sagittal section and measured in the largest anterior–posterior diameter in the fundal region. Endometrial patterns (i.e. trilaminar, homogeneous, or incompletely trilaminar TVUS appearance) were recorded. Measurements were taken during each hospital visit; and the last reading before embryo transfer was used in statistical analysis.

Assessment of embryos and embryo transfer

Rating of the best embryo quality in a cohort was assessed at the time of transfer using a graded numbering system as follows: 1.0 (symmetrical, no fragmentation), 1.5 [slight fragmentation (<10%)], 2.0 [moderate fragmentation (>15%)], 2.5 [excessive fragmentation (>25%)]. Two catheters were used: the Wallace (Marlow Surgical Technologies, Willoughby, OH, USA) and Tomcat (Sherwood, St. Louis, MO, USA). Ease of embryo transfer was noted as easy, moderate, or difficult at the time of transfer based on the descriptions of the physician and the impressions of the embryologist; as such, it was a subjective recording. However, the ease of transfer was somewhat related to catheter choice, because the Wallace was routinely used in the trial catheterizations, with the Tomcat chosen only when the Wallace could not be manipulated into the uterus.

Past history

Past history of intrauterine abnormalities, as documented by hysteroscopy or hysterosalpingogram (HSG), was recorded and correlated with embryo implantation outcome. Past medical conditions that affect the endometrium, i.e. endometritis, were also noted. Intrauterine surgery that involved the endometrium was also evaluated in relation to pregnancy outcome.

Assays

In group I patients, serum oestradiol concentrations were quantified by radioimmunoassay using Coat-a-Count kits (Diagnostic Production Corporation, Los Angeles, CA, USA) as previously described (Schmidt-Sarosi *et al*., 1995). The interassay coefficient of variation was 11.0% and the intra-assay coefficients of variation were <5% for this radioimmunoassay. Only the oestradiol measurement on the day of HCG administration was used in statistical analysis.

Colour Doppler imaging

Uterine artery colour Doppler imaging data were collected prospectively on patients in groups II–IV between March 1994 and August 1995. Data were collected only on patients in groups II–IV, in order to focus on the condition of the uterus, since these patients had suppressed or inactive ovaries and were hormonally similar. A subgroup of 30 patients (group II, $n = 16$; group III, $n = 7$; group IV, $n = 7$) had a complete work-up, including colour Doppler imaging, measurements of uterine artery peak systolic velocity (PSV) and resistance index (RI) as well as endometrial thickness, and this group subsequently had a total of 14 pregnancies. The measurements were obtained by pulsed Doppler spectral analysis. The PSV and RI for both uterine arteries were obtained. Measurements from the last scan before embryo transfer were used in statistical analysis.

Table I. Comparison of various parameters in pregnant versus non-pregnant patients in group I

	Pregnant	Non-pregnant	*P* value
No. of embryos transferred	4.36 ± 0.23	4.11 ± 0.16	0.0575
Highest embryo grade	1.22 ± 0.32	1.38 ± 0.42	0.0104
Endometrial thickness (mm)	12.1 ± 2.6	11.0 ± 2.9	0.0065
Serum oestradiol at HCG (pg/ml)	1981.4 ± 121.3	1544.1 ± 85.4	0.0068
Catheter type[a]: Wallace	76.4% (55/72)	60.0% (81/135)	0.0270
Tomcat	23.6% (17/72)	40.0% (54/135)	

[a]Pearson's c^2 test.

Pregnancy outcome

Clinical pregnancy was defined as a positive serum β-HCG titre (>5 mIU/ml, Coat-a-Count kit radioimmunoassay; Diagnostic Production Corporation) with a corresponding TVUS-confirmed intrauterine gestational sac. The β-HCG titre was assessed 2 weeks post-embryo transfer.

Statistical analysis

Means and SEM were calculated. After testing for normality with the Kolmogorov–Smirnov test [Sigmastat, Jandel Scientific Software; Jandel Corporation, San Rafael, CA, USA], a variable distribution of normal populations was found. Therefore data were processed using non-parametric tests for comparing either two groups (Mann–Whitney rank sum test) or three or more groups (Kruskal–Wallis analysis of variance on ranks). Frequency analysis was performed with either Pearson's c^2 or Fischer's Exact test, depending on the number of observations per group, to identify significance ($P < 0.05$) between groups. Coefficients of correlation (r values) were used where appropriate. Student's t-test was used where appropriate.

Results

Group I

Cycles resulting in a positive pregnancy outcome had a statistically significant higher embryo grade than those resulting in non-pregnant outcomes ($P = 0.0104$). The top embryo grade in non-pregnant patients was 1.38 ± 0.42 (range 1.0–2.5), whereas in pregnant patients it was 1.22 ± 0.32 (range 1.0–2.0). Serum oestradiol concentrations at the time of HCG administration were also significantly greater in pregnant (1981.4 ± 121.3 pg/ml) than in non-pregnant (1544.1 ± 85.4 pg/ml) cycles ($P = 0.0068$; Table I).

Statistical analysis of the group I data revealed significantly thicker TVUS-endometrial measurements in pregnant versus non-pregnant cycles ($P = 0.0065$). Mean endometrial thickness for non-pregnant patients was 11.0 ± 2.9 mm (range 3.4–19.0), while that for pregnant patients was 12.1 ± 2.6 mm (range 6.8–19.0). Of the 72 pregnant patients, the Wallace catheter was used in 55 (76.4%), whereas the Tomcat was used in 17 (23.6%). Of the 135 non-pregnant patients, the Wallace was used in 81 (60.0%), while the Tomcat was used in 54 (40.0%) ($P = 0.0270$). No differences were noted

Table II. Comparison of factors between group II (n = 38), III (n = 12) and IV (n = 8). Data expressed as mean ± SEM

	Group II	Group III	Group IV	P value
Age of patient undergoing embryo transfer (years)	33.8 ± 4.12	44.0 ± 2.0	44.3 ± 0.9	0.00000014
Age of oocyte supplier (years)	33.8 ± 4.2	26.5 ± 4.2	26.4 ± 5.3	0.000024
No. of embryos transferred	3.4 ± 1.5	3.8 ± 1.0	3.3 ± 0.9	0.324
Highest embryo grade	1.40 ± 0.42	1.08 ± 0.20	1.38 ± 0.58	0.0877
Endometrial thickness (mm)	9.0 ± 2.1	8.5 ± 0.8	8.7 ± 0.8	0.544
Weeks of oestradiol regimen	3.5 ± 1.2	2.7 ± 0.8	3.8 ± 1.7	0.131
Pregnancy rate[a]	24.0% (6/25)	41.7% (5/12)	37.5% (3/8)	0.199

[a]Pearson's c^2 test.

between the pregnant versus non-pregnant groups in the number of embryos transferred (P = 0.0575) or ease of transfer (P = 0.119). The overall pregnancy rate (the number of pregnancies per retrieval) was 33.6% (72/214). Ten patients did not undergo an embryo transfer. There were two ectopic pregnancies (one with a Tomcat and one with a Wallace catheter) that were excluded.

The minimum TVUS-measured endometrial thickness to achieve pregnancy was 6.8 mm. Of the non-pregnant patients, only 8/142 (5.6%) had an endometrium <6.8 mm. Among patients with an endometrial thickness >6.8 mm, 65% (134/206) did not achieve a pregnancy, while 35% (72/206) had a positive pregnancy outcome.

Group III versus IV

Analysis of groups III and IV revealed similar pregnancy rates (P = 0.199), with 41.7% (5/12) pregnant in group III, and 37.5% (3/8) in group IV (Table II). No statistically significant differences between groups III and IV were apparent in the number of embryos transferred (P = 0.257), endometrial thickness (P = 0.937), embryo quality (P = 0.122), number of weeks of oestradiol treatment (P = 0.0602) or patient (P = 0.777) or donor (P = 1.000) age.

Groups II–IV

Because groups II, III and IV underwent similar protocols, important factors were statistically compared to justify combining the three groups for later analysis (Table II). Only the ages of the patient and oocyte donor were statistically different; however, because the older patients received embryos derived from oocytes from younger donors, the three groups were suitably matched. The final combined group (II–IV) consisted of 52 cycles resulting in 14 pregnancies, or a 26.9% pregnancy rate.

Statistically significant differences between pregnant and non-pregnant patients were apparent in the rating of the top embryo quality (P = 0.042; Table III) and ease of transfer (P = 0.029). There were no significant differences between pregnant and non-pregnant cycles for endometrial thickness (P = 0.74), number of embryos transferred (P = 0.49), or number of weeks of oestradiol treatment (P = 0.26, with a range of 2.0–5.5 weeks in non-pregnant and 2–6 weeks in subsequently pregnant patients; Table III).

Among the pregnant patients, 80.0% (12/14) had the triple echogenic pattern and 13.3% (2/14) were incompletely homogeneous (a mix of hyperechogenic and hypoechogenic), with one pregnancy resulting in a spontaneous abortion. Only one patient had a clinical pregnancy on a homogeneous endometrium, but she spontaneously aborted. Similar distributions of endometrial TVUS pattern were observed in the non-pregnant group: homogeneous in 11.6% (5/43), incompletely homogeneous in 2.3% (1/43), and triple in 83.7% (36/43). The pattern was not recorded for one patient.

Table III. Comparison of various parameters in pregnant versus non-pregnant patients in groups II–IV

	Pregnant	Non-pregnant	P value
No. of embryos transferred	3.9 ± 0.5	3.5 ± 0.2	0.49
Highest embryo grade	1.1 ± 0.1	1.4 ± 0.1	0.042
Endometrial thickness (mm)	9.1 ± 0.7	8.6 ± 0.4	0.74
Weeks of oestradiol regimen	3.7 ± 0.4	3.2 ± 0.2	0.26
Catheter type[a]: Wallace	92.9% (13/14)	77.4% (24/31)	0.402
Tomcat	7.1% (1/14)	22.6% (7/31)	

[a]Fisher's exact test.

Table IV. Mean rating of highest embryo grade (Student's t-test)

	Pregnant		Non-pregnant		P value
	n	mean ± SEM	n	mean ± SEM	
Group II	6	1.17 ± 0.1	19	1.39 ± 0.08	0.21
Group III	5	1.00 ± 0.0	7	1.14 ± 0.09	0.43
Group IV	3	1.17 ± 0.2	5	1.50 ± 0.3	0.79

The top embryo grade for non-pregnant patients was 1.40 ± 0.1 (range 1.0–2.5), while that for pregnant patients was 1.1 ± 0.1 (range 1.0–1.5). Since the top quality embryo grade was significantly better in the pregnant versus non-pregnant subgroups from the combined groups II–IV, the highest embryo grade in the component groups was individually analysed. However, no statistically significant differences were observed in the pregnant cycles in each of the groups (Table IV), despite the fact that embryo grade in the pregnant group appeared marginally better than that in the non-pregnant group. A larger sample is necessary to determine statistical significance.

Data for past history of uterine surgery and medical conditions were analysed per patient rather than per cycle for 31 non-pregnant and 14 pregnant patients in groups II–IV (Table V). Two patients had relevant endometrial medical conditions, one pregnant (1/31, or 3.2%) with a past history of endometritis

Table V. Past history of uterine surgery and/or abnormalities in groups II–IV

	Pregnant		Non-pregnant	
	No.	%	No.	%
Medical conditions	1/14	7.1	1/31	3.2
Infected IUD	0/14	0	1/31	3.2
Endometritis/TB	1/14	7.1	0/31	0
Hysteroscopy	4/14	28.6	8/31	25.8
Surgical procedures	3/14	21.4	6/31	19.4
Myomectomy	0/14	0	2/31	6.9
Polypectomy	1/14	7.1	1/31	3.2
Lysis of adhesions	1/14	7.1	1/31	3.2
Curettage of atrophic cornu	1/14	7.1	1/31	3.2
Resection of septum	0/14	0	1/31	3.2
Hysterosalpingogram (abnormal)	5/14	35.2	9/31	29.0
Endometrial polyp	1/14	7.1	0/31	0
Intrauterine adhesion	1/14	7.1	4/31	12.9
Submucosal fibroid	0/14	0	2/31	6.5
T-shaped uterus	2/14	14.3	2/31	6.5
Bicornual uterus	0/14	0	1/31	3.2
Unicornate uterus	1/14	7.1	0/31	0
Hysterosalpingogram (normal)	0/14	0	1/31	3.2

from an infected intrauterine device, and one non-pregnant (1/14, or 7.1%) with past endometritis secondary to tuberculosis. Hysteroscopies had been performed on 25.8% (8/31) of non-pregnant patients and 28.6% (4/14) of pregnant patients. Of these, 19.4% (6/31) non-pregnant and 21.4% (3/14) pregnant patients had had a surgical procedure performed. Nine non-pregnant (29.0%) and five pregnant (35.7%) patients had previously undergone an HSG with abnormal findings such as uterine leiomyomata, adhesions and uterine malformations (Table V).

Group I versus groups II–IV

A comparison of endometrial thickness (4 days prior to embryo transfer) of group I with groups II–IV resulted in a statistically significant difference in both non-pregnant ($P = 0.00001$; means: group I = 11.0 ± 2.9 mm, groups II–IV = 8.48 ± 0.34 mm) and pregnant ($P = 0.0002$; means: group I = 12.1 ± 2.6 mm, groups II–IV = 9.19 ± 0.58 mm) cycles.

Uterine artery colour Doppler imaging TVUS in patients in groups II–IV

Since there were no statistically significant differences between the means of the right and left uterine artery Doppler measurements (RI: $P = 0.3232$; PSV: $P = 0.8459$), the mean of the right and left uterine arteries for each patient was used in the analyses. There were no significant differences between pregnant and non-pregnant patients for any of the tested parameters of the mean uterine artery colour Doppler imaging TVUS data (Table VI). A graph of PSV plotted against endometrial thickness gave a coefficient of correlation (r value) of 0.277 in non-pregnant patients and 0.189 in pregnant patients. Average RI versus endometrial thickness resulted in $r = 0.216$ for non-pregnant and $r = 0.502$ for pregnant patients.

Twelve patients who underwent a minimum of two scans plus the baseline scan were examined longitudinally for a correlation with length of oestradiol administration. There was no apparent relationship between the length of oestradiol treatment and mean uterine artery RI or PSV, or between pregnant and non-pregnant patients, with r values <0.1 (data not shown).

Discussion

We found that the most consistent factor for predicting pregnancy rates was the quality of the best-rated embryo. This holds true for both ovary-stimulated cycles (group I) and ovary-independent cycles (groups II–IV). Past studies have resulted in similar conclusions (deZiegler and Frydman, 1990; Grillo *et al*., 1991; Bernardini *et al*., 1993; Visser and Fourie, 1993). However, the importance of embryo quality in determining pregnancy outcome should not be considered independently of other factors. Many unsuccessful cycles had an embryo rated as high quality (1.0), while poorly rated embryos (2.0) did successfully implant. Therefore, while these results can be used as guidelines, they cannot be absolute indicators of when to terminate a cycle.

The similar pregnancy rates of groups III and IV further emphasize the importance of embryo quality, since the embryos of group IV were able to survive cryopreservation and thawing without reduction of pregnancy rate. A previous study similarly found that high-quality embryos could withstand freezing without detriment to the pregnancy potential (Selick *et al*., 1995). Other past research has suggested that cryopreservation of embryos results in a lower pregnancy rate (Society for Assisted Reproductive Technology, 1995). In groups III and IV, however, this was not observed, probably because the oocyte quality upon retrieval was high enough to permit the embryos to survive a thaw cycle and successfully implant.

In group I, the endometrium was significantly thicker in pregnant patients than in non-pregnant ones, whereas there was no significant difference in groups II–IV. Group I underwent ovarian stimulation and, therefore, the endometrial thickness may be more reflective of the endogenous hormonal environment, which in turn may be related to oocyte and thus embryo quality. Groups II–IV received only exogenous oestrogen to prime the uterus, endogenous oestrogen being either suppressed with GnRH agonists or absent because of ovarian failure. Thus, the endometrium remained detached from the hormonal environment of the other reproductive organs. The significant difference in endometrial thickness between group I and groups II–IV confirms the difference in hormonal environment, since the group I endometrium was substantially thicker (⩾2 mm) than that of groups II–IV.

The chance of pregnancy increased with a thicker endometrium, but the range of thickness in pregnant and non-pregnant cycles overlapped extensively (the whole pregnant range was encompassed in the non-pregnant range). While overall the chance of successful implantation was better with a thicker endometrium, an endometrial thickness ⩾6.8 mm can result in pregnancy, thicknesses less than this probably being inadequate for implantation. A triple echogenic endometrial pattern on TVUS was most favourable for both establishing and continuing a pregnancy. Patients with incomplete patterns were less likely to carry a pregnancy to term, but this was still

Table VI. Colour Doppler data (Student's *t*-test)

	Pregnant		Non-pregnant		*P* value
	n	mean ± SEM	*n*	mean ± SEM	
Patient's age (years)	9	39.6 ± 2.2	21	38.1 ± 1.5	0.611
Average PSV	9	43.64 ± 15.95	21	40.44 ± 14.60	0.596
Average RI	9	0.77 ± 0.09	21	0.79 ± 0.11	0.596
Endometrial thickness (mm)	9	8.2 ± 0.6	21	7.9 ± 0.4	0.690

PSV = peak systolic velocity (cm/s); RI = resistance index.

possible. A homogeneous pattern was sufficient to establish a pregnancy, but inadequate to maintain it.

Past research has failed to find a consistent role of endometrial monitoring in predicting pregnancy outcome in IVF cycles. Several investigators concluded that endometrial thickness was not different between subsequently pregnant and non-pregnant cycles (Fleisher *et al.*, 1986; Oliveira *et al.*, 1993; Coulam *et al.*, 1994). Others did find a difference, with a thicker endometrium among subsequently pregnant patients (Gonen *et al.*, 1989; Check *et al.*, 1993; Noyes *et al.*, 1995). Some studies have proposed a cut-off level at which endometrial thickness becomes appropriate for implantation, either at ⩾6 mm (Shapiro *et al.*, 1993; Coulam *et al.*, 1994), ⩾10 mm (Check *et al.*, 1991, 1993; Check, 1994), or ⩾13 mm (Rabinowitz *et al.*, 1986). Echogenicity patterns of the endometrium have been studied by many investigators, most of whom agree that a triple or mixed (incomplete) pattern can sustain pregnancy, while a homogeneous pattern cannot (Check *et al.*, 1991; Ueno *et al.*, 1991; Sher *et al.*, 1993; Coulam *et al.*, 1994; Serafini *et al.*, 1994).

The lack of a statistically significant difference in the number of weeks of oestradiol treatment between pregnant and non-pregnant patients in groups II–IV is not surprising, since the patients were not on a set protocol for length of treatment. Instead, patients continued to receive oestradiol to reach their highest possible endometrial thickness. With a goal of ⩾8 mm, some of the patients responded quickly to treatment and had a shorter oestradiol regimen, while others still did not reach this thickness after more than a month of treatment. The group of patients who were quicker to respond to oestradiol achieved a similar number of pregnancies as patients who were slow to respond. Thus, the ability of the patients to respond to oestradiol, and not the amount of time required to do so, was the important aspect for successful implantation.

Among group I patients, the significantly higher serum oestradiol concentrations in pregnant patients reflects both the embryo quality and endometrial receptivity. This is a reflection of the follicular development of stimulated ovaries, where higher oestradiol concentrations are correlated with a greater number of follicles and more mature oocytes. Also, it directly impacts on the proliferation of the endometrium, so that an overall thicker endometrium is probably related to a higher oestradiol concentration.

Previous uterine surgery had no effect on ability to establish a pregnancy, since an even greater percentage of subsequently pregnant patients than of non-pregnant patients had a history of operative hysteroscopy or abnormal HSG. Patients with a scarred endometrium from past endometritis were found in both the pregnant and non-pregnant outcome groups. This observation, in conjunction with the apparent lack of correlation between endometrial thickness and pregnancy rate in groups II–IV, suggests that the condition of the embryo, not the uterus, may be the major determining factor of pregnancy in patients who do not undergo ovarian stimulation. Furthermore, the beneficial effect of removing intrauterine pathology may outweigh the potentially adverse effect of inadvertent endometrial scarring on implantation and pregnancy outcome.

The TVUS uterine artery colour Doppler imaging data also had no apparent predictive value for pregnancy. Our results show that neither RI nor PSV had predictive values in relation to endometrial thickness or length of oestradiol treatment. This may be due to the nature of uterine artery Doppler measurements, which are based on flow to the entire uterus, not to focal areas of the endometrium. For implantation of an embryo to establish a successful pregnancy, however, the quality of the endometrium at the exact location of implantation may be more important than the global blood flow throughout the uterus. Because RI and PSV may not be predictive of the flow to the focal area of the endometrium at which the embryo implants, these data may be of limited value.

In contrast to our study, several past studies on colour Doppler imaging have concluded that there is a predictive value in uterine artery impedance. Several of these studies used the pulsatility index (PI) as the measure of impedance and determined that a PI of <3 (Steer *et al.*, 1992) or <3.3 (Coulam *et al.*, 1994) was more favourable for pregnancy, although they did not uniformly support the notion of PI cut-off levels (Tekay *et al.*, 1995). RI was determined to be significantly lower at the time of oocyte aspiration in subsequently pregnant patients by Sterzik *et al.* (1989). However, this study could not be directly correlated with ours, as our Doppler patients did not undergo controlled ovarian stimulation. Another study (Serafini *et al.*, 1994) did find a significant difference in RI between pregnant and non-pregnant cycles, but concluded that uterine blood flow had less predictive value than other endometrial indicators (e.g. echogenic pattern). No published studies to date have addressed the predictive value of PSV.

From our examination of both ovarian-dependent and -independent IVF cycles, we conclude that embryo quality is the best predictor of pregnancy outcome. The endometrial thickness in stimulated cycles is predictive probably because it is reflective of the hormonal milieu (as also supported by our peak oestradiol data), compared with the ovary-independent cycles, where this is not found. The length of oestradiol administration was related not to pregnancy outcome but to individual patient responsiveness. Uterine artery colour Doppler imaging parameters do not seem to be predictive of pregnancy outcome. A past history of uterine surgery or endometritis also did not significantly affect the pregnancy rate.

Acknowledgement

We acknowledge Dr F.Licciardi's clinical care of some of the patients included in this study.

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Received on January 31, 1996; accepted on October 17, 1996