

Preliminary report of an ultrasonography and colour Doppler uterine score to predict uterine receptivity in an in-vitro fertilization programme

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A total of 96 women undergoing in-vitro fertilization (IVF) treatment were examined by transvaginal ultrasonography with colour and pulsed Doppler ultrasound on the 22nd day of the menstrual cycle preceding IVF. We assessed endometrial thickness, endometrial morphology, myometrial echogenicity, subendometrial vascularization, the uterine artery pulsatility index, protodiastolic notch and end diastolic blood flow in order to define a uterine score which could be correlated with the pregnancy rate. The overall pregnancy rate was 30.2%, and there was no difference between the pregnant and non-pregnant groups with regard to any of the ultrasonographic and Doppler parameters when examined separately. However, the uterine score was significantly higher in the pregnant group (15.9 ± 2.81 versus 12.7 ± 5.3 , $P = 0.002$; *t*-test). No pregnancy occurred if the score was between 0 and 10. With a score of 11–15 there was a 34.7% chance of pregnancy, and scores >16 had a 42% chance of pregnancy. In conclusion, individual ultrasonographic and Doppler parameters are not of sufficient accuracy to predict uterine receptivity. The uterine score calculated prior to IVF cycles appears to be a useful predictor of implantation.
Key words: endometrial receptivity/colour Doppler/transvaginal ultrasonography/uterine arteries

Introduction

Successful implantation during in-vitro fertilization (IVF) and embryo transfer depends on many factors including embryo quality and uterine receptivity. Transvaginal ultrasonography plays an essential role in modern fertility management. In the context of IVF the transducer allows easy monitoring of follicular and endometrial growth, inspection of uterine, ovarian and endometrial morphology and easy access to the ovaries for the procedure of oocyte retrieval. In recent years attempts have been made to simplify IVF treatment (Wilkland *et al.*, 1994) and improve pregnancy rate by the use of gonadotrophin releasing hormone agonists, but the implantation rate per embryo transferred remains ~10–15%.

Although it is well known that there are multiple factors

which influence successful implantation (Edwards and Steptoe, 1983), there is much debate regarding the relationship of endometrial thickness and morphology to successful implantation in IVF programmes (Gonen and Casper, 1990). Many teams have reported significant correlations between pregnancy rate and endometrial thickness (Fleisher *et al.*, 1991) and morphology as defined by ultrasonography, while others have failed to demonstrate such relationships. Recently, the measurement of impedance to uterine artery blood flow in IVF cycles has provided an indirect estimation of endometrial receptivity (Steer *et al.*, 1992). The impedance of blood flow through the uterine arteries may be expressed as the pulsatility index (PI). The PI may be classified as low, medium and high in the ranges 0.00–1.99, 2.00–2.99 and ≥ 3 respectively. Many teams have reported a significant decrease in PI in patients in whom pregnancy follows IVF (Bied-Damon *et al.*, 1995), whereas others have failed to show such modifications of PI in cases of embryo implantation (Favre *et al.*, 1993).

A more logical approach would be to analyse all the ultrasonographic and Doppler parameters together in order to assess uterine receptivity (Ziegler *et al.*, 1992). In this prospective study we aimed to examine the ability of an ultrasonography score to assess the uterine receptivity. This score includes endometrial parameters (thickness and pattern), myometrial echogenicity, uterine artery blood flow parameters (PI, protodiastolic notch, end diastolic blood flow) and subendometrial vascularization.

Materials and methods

Over the last 5 months of 1996, all patients underwent transvaginal ultrasonography on the 22nd day of the menstrual cycle the month before IVF in order to assess uterine receptivity. All had regular, ovulating, menstrual cycles confirmed by temperature graph. All had a normal serum follicle stimulating hormone (FSH) on day 3 of the cycle. Women >38 years old were not included in this study. All ultrasound scans were performed using a 5 MHz endovaginal probe for B mode, colour and pulsed Doppler examinations (Ultra Mark 9 ATL). The procedure was the same as that previously described (Salle *et al.*, 1996). The spatial peak temporal average intensity of ultrasound B mode and Doppler examinations was <50 mW/cm². The maximum sensitivity for the detection of blood flow was set at 3.0 cm/s. All ultrasound scans were performed by either B.S. or V.B.D.

The maximum thickness of the endometrium was measured as the maximum distance between each myometrial/endometrial interface through the central longitudinal axis of the uterus. An endometrial thickness >7 mm was considered as normal and scored 3. The endometrial morphology was assessed according to the classification proposed by Gonen and Casper (1990). A multilayered endometrium, consisting of a prominent outer and central hyperechogenic line and inner hypoechogenic region was considered as normal and scored 3.

Table I. The uterine scoring system

Parameter	Score
Endometrial thickness	
<7 mm	0
≥7 mm	3
Endometrial pattern	
Multilayered endometrium	3
Others	0
Myometrial echogenicity	
Homogeneous	1
Non-homogeneous	0
Uterine artery PI	
≤3	4
>3	0
Protodiastolic notch	
Present	0
Absent	2
End diastolic blood flow	
Present	4
Absent	0
Endometrial blood flow	
Present	3
Absent	0
Total	20

PI = pulsatility index.

The uterine artery PI was measured on a transverse scan through the uterine isthmus. PI was measured from the maximum frequency envelope as follows: $PI = (S - D)/\text{mean}$, where S is the peak systolic Doppler shifted frequency, D is the minimum diastolic Doppler shifted frequency and the mean is the mean maximum Doppler shifted frequency over the cardiac cycle. In this position the flow velocity waveforms of both uterine arteries can be studied as previously described. As in previous studies (Favre *et al.*, 1993; Bied-Damon *et al.*, 1996), PI was classified as normal if ≤ 3 and scored 4. The pattern of the uterine artery spectrum was studied during three cardiac cycles. A pattern was considered to be adequate if the protodiastolic notch was absent and scored 2. If the end diastolic blood flow could be observed a score of 4 was entered. Endometrial vascularization was assessed on a longitudinal scan of the uterus. The colour gate was placed over the thickest part of the endometrium. The presence or absence of colour in the subendometrial region was determined. The vascularization was considered as positive and scored 3 if more than three vessels penetrating the outer hypoechogenic area surrounding the endometrium could be seen.

The myometrium was studied on a longitudinal scan of the uterus. Myometrium was considered to be appropriate if completely homogeneous and scored 1. The value of each parameter was determined according to the literature on ultrasonic parameters in IVF. There has been global agreement on the values of endometrium pattern and thickness. We have previously shown (Bied-Damon *et al.*, 1995) that $PI > 3$ is unfavourable to embryo implantation. End diastolic blood flow and endometrial blood flow have previously been correlated with implantation rate and appear to be related to endometrial maturity. Myometrial echogenicity is important for the global analysis of the uterus but it is not essential for implantation. The uterine scoring system includes all of the following parameters: endometrial thickness, endometrial pattern, myometrial echogenicity, uterine artery PI, notch protodiastolic, end diastolic blood flow, endometrial vascularization. Each parameter is scored as shown in Table I. The procedure is easy and can be performed in 10 min.

All of the patients subsequently underwent IVF treatment. Each patient received triptoreline (Décapeptyl; Ipsen Biotech, Paris, France)

starting on day 1 or 22 of the menstrual cycle. After 3 weeks of triptoreline, serum oestradiol and luteinizing hormone (LH) concentrations were measured to ascertain whether adequate gonadotrophin suppression had been achieved (oestradiol < 30 pg/ml). Ultrasonography was performed on the same day to rule out ovarian cysts. If either the serum concentrations or sonogram were inadequate they were repeated 1 week later. If both measurements were adequate human menopausal gonadotrophin (HMG, 300 UI/day) was administered. Vaginal sonography was performed and serum oestradiol and LH concentrations were measured daily after 5 days of HMG. The dosage of HMG was adjusted, if necessary, according to serum oestradiol concentrations and size of the follicles. Human chorionic gonadotrophin (HCG, 5000 UI Chorionic Gonadotrophin 'Endo'; Organon, Paris, France) was administered when a minimum of two lead follicles with an 18 mm average diameter were seen sonographically and when the serum oestradiol was ≥ 300 pg/ml per follicle. Oocyte retrieval was carried out by the vaginal route with sonographic guidance and general anaesthesia 36 h after HCG administration. Forty-eight hours after oocyte retrieval, a maximum of two or three embryos was transferred. Progesterone (Utrogestan; Besins Iscovesco, Paris, France) was prescribed for 16 days for luteal support. Serum β HCG was measured 14 days after embryo transfer to diagnose pregnancy. If the pregnancy test was positive, luteal support was continued. The transvaginal ultrasonography was performed 4 weeks later, to diagnose a clinical pregnancy. The pregnancy rate was defined as the proportion of women achieving a clinical pregnancy 4 weeks after embryo transfer, and this was then related to the ultrasonographic score, to the colour Doppler parameter and to the uterine score.

Statistical methods

All data were entered into a computer and analysed with Unistat analysis (Unistat, London, UK). Data presented are mean \pm SD. The Student's t -test and χ^2 -analysis were used as appropriate. $P < 0.05$ was considered significant.

Results

Our study included 96 patients. The pregnancy rate was 30.2%. There were no significant differences between the pregnant and the non-pregnant groups for the date of the echography, the age of the patients, the number of HMG ampoules, the serum oestradiol concentration, the day on which HCG was administered, the number of follicles aspirated, the number of oocytes fertilized or the number and quality of the embryos transferred (Table II). The number of oocytes retrieved was significantly higher in the pregnant group (Table II).

In addition there was no significant difference in the echographic parameters (Table III) for endometrial thickness or the uterine pulsatility index between the pregnant and non-pregnant groups (t -test). The echographic appearance of the endometrium (Table III), the presence or absence of a protodiastolic notch and the end diastolic blood flow were identical in the two groups (χ^2 -test). The only significant difference was the uterine echographic score which was higher in patients who became pregnant [15.9 ± 2.81 versus 12.7 ± 5.3 , $P = 0.002$ (t -test), Table III].

No pregnancy occurred if the echographic score was between 0 and 10 range. With a score of 11–15 there was a 34.7% chance of pregnancy, and patients who had a uterine score > 16 had a 42% chance of pregnancy.

Table II. Clinical details of pregnant and non-pregnant patients

	Pregnant (mean \pm SD)	Non-pregnant (mean \pm SD)	Significance (<i>t</i> -test)
Menstrual day of ultrasound	22.2	22.5	NS
Age (years)	30.6 \pm 4.7	32.1 \pm 4.5	NS
Ampoules HMG (<i>n</i>)	36.7 \pm 19.9	34.5 \pm 17.1	NS
Day of HCG administration	12.2 \pm 2.0	12.0 \pm 1.8	NS
Serum oestradiol (pmol/l)	1919.0 \pm 706.19	1699.4 \pm 1011.3	NS
Viable oocytes retrieved (<i>n</i>)	16.8 \pm 7.4	12.9 \pm 7.4	<i>P</i> < 0.05
Oocytes fertilized (<i>n</i>)	8.9 \pm 7.7	6.9 \pm 4.8	NS
Embryos transferred (<i>n</i>)	2.81 \pm 0.4	2.65 \pm 0.7	NS

HMG = human menopausal gonadotrophin; HCG = human chorionic gonadotrophin; NS = non-significant.

Table III. Ultrasound details of pregnant and non-pregnant patients

Parameter	Pregnant	Non-pregnant	<i>P</i>
Uterine score	15.9 \pm 2.81	12.7 \pm 5.3	0.002 (<i>t</i> -test)
Endometrial thickness (\geq 7 mm)	8.54 \pm 1.5	8.14 \pm 3.11	0.51 (<i>t</i> -test)
Endometrial pattern (multilayered)	0.79%	0.68%	0.24 (χ^2)
Myometrial echogenicity (homogeneous)	0.82%	0.68%	0.77 (χ^2)
Uterine artery PI (\leq 3)	2.56 \pm 0.53	2.75 \pm 0.64	0.12 (<i>t</i> -test)
Protodiastolic notch (absent)	0.31%	0.29%	0.78 (χ^2)
End diastolic blood flow (present)	0.96%	0.80%	0.30 (χ^2)
Endometrial blood flow (present)	0.79%	0.56%	0.27 (χ^2)

PI = pulsatile index.

Table IV. Pregnancy distribution according to the value of the uterine score

Score	<i>n</i>	Pregnant	Pregnancy rate (%)
0-5	9	0	0
6-10	12	0	0
11-15	35	12	34
16-20	40	17	42

Nine patients had a score of 0-5 range, 12 patients had a score of 6-10; 35 and 40 patients had a score of 11-15 and 16-20 respectively. In 26 patients the PI was $>$ 3. There were only two pregnancies (0.07 %) among these patients. Thirteen had no end diastolic flow and only one of these patients achieved a pregnancy (7.6 %). In 35 patients it was not possible to demonstrate subendometrial vascularization and in this group there were only six pregnancies (17.1%).

Discussion

All authors agree on the importance of precise and specific endometrial maturation for implantation during IVF.

The standard method of endometrial dating is the histological evaluation of an endometrial biopsy specimen (Noyes *et al.*, 1950). Obviously, the invasiveness of this procedure is not acceptable in the clinical context of IVF. As echography is non-invasive, easily repeatable and specific, the use of high resolution ultrasonography has quite naturally found its place in endometrial assessment. The two parameters studied by echography are endometrial thickness and morphology.

Friedler *et al.* (1996), in their review of 22 studies which included 4256 cycles, have analysed the role of ultrasonography

in the evaluation of uterine receptivity. Endometrial thickness is easy to measure by echography and bears no relationship to the echographic aspect of the endometrium. The first question to be posed is whether endometrial thickness is greater in conception cycles. In 16 of the 22 studies that Friedler (1996) examined, there was no significant difference between conception and non-conception cycles. Thus, there was no ideal range for endometrial thickness. Of the 1605 cycles investigated by Friedler (1996), 504 of which were conceptional, the mean endometrial thickness was virtually the same in conception and non-conception cycles: 8.66-11.8 and 8.6-11.9 mm respectively. Finally, the only point on which all investigations of endometrial thickness concur is that the endometrium must be sufficiently thick to enable embryonic implantation. According to different studies this thickness varies from 6 to 8 mm. Our results are in agreement with the literature (Coulam *et al.*, 1994), as we have never obtained pregnancies when endometrial thickness was $<$ 7 mm.

The criticisms that apply to endometrial thickness also apply to echographic endometrial pattern. Friedler *et al.* (1996) reported 13 studies where there were significant differences between conception and non-conception cycles and nine studies where no differences were found. A multilayered endometrium may be the sonographically determined parameter that most accurately reflects endometrial receptivity (Sefarini *et al.*, 1994).

Recently, measurement of the impedance in the uterine artery during IVF has provided an indirect assessment of uterine receptivity. We have previously reported a significantly lower pulsatility index when pregnancy was achieved following IVF (Bied-Damon *et al.*, 1995). No pregnancies were achieved if the PI was $>$ 3.5 on the day of embryo transfer. Colour

Doppler analysis allows an assessment of the impedance of the vascular flow of the uterine artery and measurement of uterine perfusion (Kupesic and Kurjak, 1993). Thus sonographic imagery has gained a physiological dimension in addition to the anatomical one. Steer *et al.* (1992) reported a significantly lower PI in cases of implantation during IVF. However, subsequent authors (Favre *et al.*, 1993; Tekay *et al.*, 1995) have observed no difference. Recently, Bloeche *et al.* (1997) reported a significantly decreased PI in a pregnancy 12 days after the embryo transfer. It is obvious that an increased blood flow supply is necessary when implantation has occurred but at this time the information given by colour Doppler on the state of the uterine artery is not clinically useful. No studies have obtained implantation when the PI was >3 (Sterzik *et al.*, 1989; Bassil *et al.*, 1995; Coulam *et al.*, 1995; Deichert *et al.*, 1996; Tekay *et al.*, 1996). If a PI upper limit for the uterine artery of 3 or 3.3 is defined, Doppler blood flow has a high negative predictive value and sensitivity (88–100 and 96–100% respectively). The positive predictive value and the specificity of uterine vascularization remain low (44–56 and 13–35 respectively); however, they are higher than results given by other echographic parameters (Friedler *et al.*, 1996).

Good uterine perfusion leads to a reduction in the vascular index during the luteal phase (Zaidi *et al.*, 1995b). During the menstrual cycle Bourne *et al.* (1996) recently showed that the PI of the uterine arteries diminishes progressively during the luteal phase, confirming the studies of Steer *et al.* (1990) and other authors (Goswany and Steptoe, 1988; Scholtes *et al.*, 1989; Kurjak *et al.*, 1991). These data suggest that an appropriate blood flow is required if a menstrual cycle is to become a potential conception cycle following coitus during the fertile period. This is the corollary of good vascular diastolic compliance which leads to the presence of the end diastolic flow. In a prospective study, Sefarini *et al.* (1994) showed that the presence of the end diastolic blood flow is a good predictive factor of clinical pregnancy and normal pregnancy following IVF and embryo transfer. The presence of the complete diastolic flow seems to be important for implantation. Few authors have examined endometrial vascularization. Zaidi *et al.* (1995a) showed that patients who did not develop sub- and intra-endometrial vascularization during induction of ovulation did not become pregnant. Endometrial vascularization is related to a positive predictive value and 100% specificity in the absence of implantation.

Doppler echography is an interesting tool for assessing uterine receptivity (Strohmer *et al.*, 1991). However, parameters studied by colour Doppler and ultrasonography are neither specific nor sensitive enough when used individually (Friedler *et al.*, 1996). Appelbaum *et al.* (1995) suggested a combination of the different echographic parameters to give a score defining uterine profile. A maximum score of 20 was always associated with conception, whereas a score <13 indicated the absence of a pregnancy. Although our results confirmed this trend, they indicated that pregnancy could still occur at a score <13 . We believe that it is important to assess uterine receptivity globally before IVF to identify those patients who have a reduced chance of successful embryonic implanta-

tion. If the uterine score is between 15 and 20 it seems logical to transfer only two viable embryos. Conversely, if the score is <5 , it may be preferable to transfer more than three embryos or to delay the transfer. In any case, sonographic parameters included in the score must be simple and easily reproduced. Unlike that of Appelbaum (1995), our scoring system is very simple. All the different parameters are scored by two variables. We have used factors derived from the literature (predictive values, sensitivity in predicting implantation outcomes) for each parameter to determine its cut-off value.

This scoring system raises some questions: is uterine receptivity in a spontaneous cycle correlated with uterine receptivity during IVF? Is it possible to correlate the uterine echographic score prior to an IVF cycle with echographic parameters assessed on the day of embryo transfer? Is it possible to improve those uterine parameters during IVF? Further research would provide the answers to these questions.

Embryonic implantation is a multifactorial phenomenon (Edwards and Steptoe, 1983). It is clear that further studies are necessary to improve our understanding of endometrial receptivity and vascular dynamics and their role in implantation. Our knowledge of morphological and vascular uterine modifications is still fragmentary (Stromer *et al.*, 1991). Clinical research could help us in our understanding and evaluation of the uterus to improve successful pregnancy rate following IVF. Uterine scoring before IVF may enable assessment of uterine receptivity.

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