Power Doppler Endometrial Evaluation as a Method for the Prognosis of Embryo Implantation in an ICSI Program

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Submitted: October 1, 1999

Accepted: February 19, 2000

Purpose: The objective of the present study was to evaluate power Doppler of the endometrium as a parameter for the prognosis of embryo implantation in patients who underwent intracytoplasmic sperm injection (ICSI).

Methods: The power Doppler was performed on a transverse section at the level of the uterine fundus on the day of human chorionic gonadotropin in 185 patients who submitted to ovarian stimulation for ICSI. The endometrium was divided into four equal quadrants and classified as grade I, II, III, or IV according to the visualization of the power Doppler in the quadrants. The color Doppler signal was considered to be positive when it reached at least the basal layer of the endometrium.

Results: Age, number of days of stimulation, number of follicles ≥ 16 mm, number of oocytes in metaphase II retrieved, and fertilization rate did not differ patients with the four different types of endometrial grades. Endometrial thickness and the pulsatility index of uterine artery also were similar for the four grades. The rate of embryo implantation also did not differ significantly ($P = 0.53$) among groups: grade I = 10%; grade II = 11.6%; grade III = 15.4%; grade IV = 10.5%. The pregnancy rates were grade I = 25%; grade II = 29.7%; grade III = 37.5%; grade IV = 23.8% ($P = 0.44$).

Conclusions: Our data demonstrate that isolated evaluation of endometrial vascularization with power Doppler is not an important factor for the prediction of pregnancy in an ICSI program.

KEY WORDS: Embryo; endometrial; ICSI; implantation; power Doppler.

INTRODUCTION

Ultrasonography is a noninvasive method that provides serial information about the characteristics of the endo-

metrium. In general, in programs of in vitro fertilization (IVF), the pattern of sound reflection (refrindex), and the thickness of the endometrial line are analyzed as factors predicting endometrial receptivity.

Some investigators have postulated the existence of a correlation between the extent of endometrial development determined by ultrasound and the probability of embryo implantation (1–5), whereas others do not consider the pattern and thickness of the endometrium to be of fundamental importance for the prediction of embryo implantation (6–9).

Transvaginal Doppler ultrasonography with or without color has been used to assess endometrial receptivity in a noninvasive manner (10–13). These studies have suggested that the impedance of uterine artery blood flow is an important parameter to determine the rates of success in an IVF program.

Power Doppler (PD) is a new modality that, unlike conventional color Doppler, maps the amplitude of the frequency shift to produce a color image. As a result, PD is more sensitive than the conventional color Doppler and enables flows with lower volumes and velocities to be displayed. In addition, PD is not affected by aliasing, which so often hampers clear images of color Doppler and can display perfused regions where the mean velocity is zero. Clearly these factors would improve visualization of small vessels (14).

Serafini *et al.* (15) reported that PD ultrasonography may permit a better evaluation of uterine receptivity than color Doppler. The objective of the present study was to test endometrial PD as a prognostic parameter for embryo implantation in patients submitted to a programme of intracytoplasmic sperm injection (ICSI).

MATERIALS AND METHODS

A total of 185 patients who underwent ovarian stimulation for ICSI were studied on the day of administra-

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tion of human chorionic gonadotropin (hCG). Ovarian stimulation before the ICSI procedure consisted of blockade of the 2nd phase with leuprolide acetate at the dose of 0.5 mg/day (Lupron, Abbott). After 14 days of treatment with the analogue and the establishment of blockade, administration of recombinant follicle-stimulating hormone (FSH) (Gonal F, Serono) was started at a fixed dose of 150 or 225 IU for a period of 7 days. On the 8th day of ovarian stimulation, we started monitoring follicular development only by vaginal ultrasound and the doses of FSH were adapted to the ovarian response. When at least three follicles measuring ≥ 17 mm in diameter were observed, hCG was administered at the dose of 10,000 IU (day 0).

On day 0, the endometrium was evaluated with a Synergy ultrasound instrument (Diasonics) with a 7.0 MHz transvaginal probe and high-resolution electronic convection. PD was used for the entire endometrium and for a small portion of the adjacent myometrium, and the fundus region was evaluated along its transverse axis.

Endometrial vascularization was classified as grades I, II, III, and IV according to the visualization of the power Doppler signal (PDS) in the corresponding quadrants, regardless of the amount of color in each quadrant (Fig. 1). The different grades were established as follows: grade I (GI) = PDS in one quadrant (24 patients); grade II (GII) = PDS in two quadrants (37 patients); grade III (GIII) = PDS in three quadrants (40 patients), and grade IV (GIV) = PDS in four quadrants (84 patients). PDS was considered to be positive when it exceeded the basal layer of the endometrium.

Oocytes were collected from the follicles 34–36 hr after hCG by transvaginal puncture guided by ultrasound. The ICSI procedure was performed by the method of Svalander *et al.* (16).

Embryo transfer (ET) was routinely performed after 48 hr in culture and supernumerary embryos were cryopreserved at the end of the second day.

Data were analyzed statistically by analysis of variance (ANOVA) and by the chi-square test.

RESULTS

Table I presents the clinical and laboratory data for the patients, divided according to grade of endometrial vascularization. Patient age was 33.7 ± 4.6 years for GI, 34.6 ± 4.6 for GII, 34.3 ± 5.1 for GIII, and 33.7 ± 4.3 for GIV. Age was similar ($P = 0.72$) for all groups.

The number of days of stimulation with FSH also did not differ ($P = 0.48$) between groups: 10.8 ± 2.5 for GI, 10.6 ± 2.1 for GII, 11.0 ± 1.8 for GIII, and 10.5 ± 1.8 for GIV. The number of follicles measuring ≥ 16 mm also was similar (0.37) for all groups: 6.2 ± 2.6 for GI, 5.8 ± 3.2 for GII, 5.5 ± 2.9 for GIII, and 6.5 ± 3.7 for GIV. The number of metaphase II oocytes also did not differ significantly between groups ($P = 0.31$): GI, 6.5 ± 3.6 ; GII, 7.2 ± 4.2 ; GIII, 6.4 ± 4.3 ; and GIV, 7.9 ± 5.0 .

The fertilization rate also was similar ($P = 0.25$) for all groups: $68.3 \pm 29.1\%$ for GI, $65.8 \pm 18.8\%$ for GII, $75.3 \pm 22.2\%$ for GIII, and $68.0 \pm 21.7\%$ for GIV. The number of transferred embryos was similar for all groups ($P = 0.64$): 2.9 ± 1.2 for GI, 3.2 ± 0.9 for GII, 3.0 ± 1.2 for GIII, and 3.1 ± 0.9 for GIV.

The pulsatility index (PI) of the uterine artery was similar ($P = 0.15$) for all groups: 2.7 ± 0.5 for GI, 2.6 ± 0.4 for GII, 2.5 ± 0.5 for GIII, and 2.4 ± 0.4 for GIV. Endometrial thickness also did not differ ($P = 0.95$) between groups: 9.5 ± 1.5 mm for GI, 9.5 ± 1.6 mm for GII, 9.3 ± 1.8 mm for GIII, and 9.5 ± 1.6 mm for GIV.

The rate of embryo implantation did not differ ($P = 0.53$) among groups: 10% (7/70) for GI, 11.6% (14/120) for GII, 15.4% (19/123) for GIII, and 10.5% (28/265) for GIV. Finally, the pregnancy rates did not differ significantly ($P = 0.44$) among groups: 25% (6/24) for GI, 29.7% (11/37) for GII, 37.5% (15/40) for GIII, and 23.8% (20/84) for GIV.

DISCUSSION

Several factors interfere with the process of embryo implantation after the application of assisted reproduction techniques. The thickness and pattern of the endometrium assessed by ultrasound during the late follicular phase have been correlated with pregnancy rates by some investigators, although this correlation was not confirmed by other groups.

Over the last few years, transvaginal ultrasound with Doppler has been used to assess uterine receptivity in IVF programs. Strohmer *et al.* (11) determined the impedance of uterine artery flow with Doppler without color on the day of hCG administration in an IVF program and found that the patients who became pregnant had significantly lower vascular impedance than the patients who were unable to become pregnant. Sterzik *et al.* (10) reported that vascular flow rate measured by the resistance index was lower in patients who became pregnant.

Fig. 1. Classification of endometrial vascularization into grades I, II, III, and IV according to the visualization of the power Doppler signal in the quadrants. GI, PDS in one quadrant; GII, PDS in two quadrants; GIII, PDS in three quadrants; GIV, PDS in four quadrants.

Table I. Clinical, Laboratory, and Ultrasonographic Results for Patients Submitted to an ICSI Program and the Various Grades of Endometrial Vascularization Observed on the Day of hCG Administration

Vascularization grade	GI	GII	GIII	GIV	<i>p</i>
Patients	24	37	40	84	
Age	33.7 ± 4.6	34.6 ± 4.6	34.3 ± 5.1	33.7 ± 4.3	0.72
No. of days of stimulation	10.8 ± 2.5	10.6 ± 2.1	11.0 ± 1.8	10.5 ± 1.8	0.48
No. of follicles ≥16 mm	6.2 ± 2.6	5.8 ± 3.2	5.5 ± 2.9	6.5 ± 3.7	0.37
No. of MII oocytes	6.5 ± 3.6	7.2 ± 4.2	6.4 ± 4.3	7.9 ± 5.0	0.31
Fertilization rate (%)	68.3 ± 29.1	65.8 ± 18.8	75.3 ± 22.2	68.0 ± 21.7	0.25
No. of embryo transfers	2.9 ± 1.2	3.2 ± 0.9	3.0 ± 1.2	3.1 ± 0.9	0.64
Pulsatility index of the uterine artery	2.7 ± 0.5	2.6 ± 0.4	2.5 ± 0.5	2.4 ± 0.4	0.15
Endometrial thickness (mm)	9.5 ± 1.5	9.5 ± 1.6	9.3 ± 1.8	9.5 ± 1.6	0.95
Implantation rate (%)	10.0	11.6	15.4	10.5	0.53
Pregnancy rate (%)	25	29.7	37.5	23.8	0.44

Recently, the introduction of color Doppler has permitted better accuracy in vessel identification. Using this technique, Steer *et al.* (12) measured uterine artery impedance on the day of ET and observed that the PI may predict uterine receptivity. They suggested that a PI > 3.0 on the day of ET could be a factor of poor prognosis. A subsequent study by Favre *et al.* (13) using Doppler on the day of ET did not confirm any difference in uterine artery PI between pregnant and nonpregnant women, but no pregnancies were obtained when PI was higher than 3.55.

In a longitudinal study on 30 patients, Tekay *et al.* (17) assessed the role of color Doppler in predicting the outcome of an IVF program and also observed no difference in uterine artery PI between pregnant and nonpregnant women. However, they observed a non-significant increase in uterine receptivity when PI was 2.0 to 2.9 on the day of embryo transfer.

Zaidi *et al.* (18) assessed endometrial thickness, endometrial morphology, presence or absence of subendometrial or intraendometrial color flow, intraendometrial vascular penetration, and subendometrial blood flow velocimetry on the day of hCG administration and related the results to pregnancy rates. The overall pregnancy rate was 32.3% (31/96), and there was no significant difference between the pregnant and nonpregnant groups with regard to endometrial thickness, subendometrial peak systolic blood flow velocity, or subendometrial PI.

In the present study, endometrial thickness did not differ ($P = 0.95$) among groups (GI = 9.5 ± 1.5 mm, GII = 9.5 ± 1.6 mm, GIII = 9.3 ± 1.8 mm, and GIV = 9.5 ± 1.6 mm), demonstrating that endometrial vascularization is not directly related to endometrial thickness.

In 1996, Zaidi *et al.* (19) determined the PI of the uterine artery on the day of hCG administration and

also found no significant difference between pregnant and nonpregnant patients, although they obtained significantly higher implantation rates when PI was less than 3.0.

Chien *et al.* (20), in a study of 108 women who underwent IVF who had at least one good-quality embryo and who were evaluated by Doppler before embryo transfer, concluded that the uterine arterial impedance measured by the Doppler sonographic examination is a noninvasive method for evaluating the endometrial response, and a mean uterine PI value of 2.5 can be used as a cutoff value to identify optimal uterine receptivity before embryo transfer.

In a color Doppler evaluation of 75 patients who had at least two cleaved embryos available for transfer, Bloechle *et al.* (21) concluded that the parameters currently used in color Doppler assessment of uterine artery perfusion are not clinically helpful in discriminating prospectively which patients will and will not become pregnant in an IVF program.

Aytoz *et al.* (22) assessed PI on the day of embryo transfer in patients who underwent an ICSI program. The patients were divided into pregnant and nonpregnant groups and were separated according to whether the PI was low (1.00–1.99), medium (2.00–2.99), or high (≥ 3.00). The PI values did not differ significantly between the pregnant and nonpregnant groups. The implantation rates were 19.5%, 15.4%, and 25% for the low, medium, and high PI groups, respectively. The ongoing pregnancy rates for the same groups were 35.3%, 26.7%, and 37.5%, respectively.

Salle *et al.* (23) assessed endometrial thickness, endometrial morphology, myometrial echogenicity, subendometrial vascularization, the uterine artery PI, protodiastolic notch, and end diastolic blood flow in a total of 96 women undergoing IVF on the 22nd day of the menstrual cycle preceding IVF and concluded

that there was no difference between the pregnant and nonpregnant groups with regard to any of the ultrasonographic and Doppler parameters when examined separately.

Our data demonstrated that the higher the PI of the uterine artery, the lower the endometrial vascularization ($GI = 2.7 \pm 0.5$; $GII = 2.6 \pm 0.4$; $GIII = 2.5 \pm 0.5$ and $GIV = 2.4 \pm 0.4$), although this difference was not statistically significant ($p = 0.15$).

Yang *et al.* (24), with the aid of PD sonography, examined the association between intraendometrial vascularity and reproductive outcome. For this study, they enrolled only women with endometrial thickness ≥ 10 mm and excluded those with apparent endometrial pathologies. Those women with an intraendometrial PD area < 5 mm² achieved a significantly lower pregnancy rate (23.5% vs. 47.5%, $P = 0.021$) and implantation rate (8.1% vs. 20.2%, $P = 0.003$) than those with an intraendometrial PD area ≥ 5 mm² and concluded that in addition to endometrial thickness the intraendometrial PD area may serve as a factor indicative of endometrial receptivity.

Dickey (25), in a review article, concluded that Doppler ultrasound measurement of uterine and ovarian blood flow is a relatively new technique. Its role in clinical medicine has yet to be established for infertility and early pregnancy. As more investigations are performed, as clinicians become familiar with its use, and as instrumentation is improved, it may yet prove to be an indispensable tool for clinical investigation of disorders of oocyte development, implantation, and early pregnancy.

Our data indicate that endometrial vascularization does not interfere with the process of embryo implantation, since evaluation of this parameter with a PD having a sensitivity three times higher than conventional Doppler (15) did not identify differences between pregnant and nonpregnant women with different patterns of vascularization.

In conclusion, our data demonstrate that isolated evaluation of endometrial vascularization with power Doppler is not an important factor for the prediction of pregnancy in an ICSI program.

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