

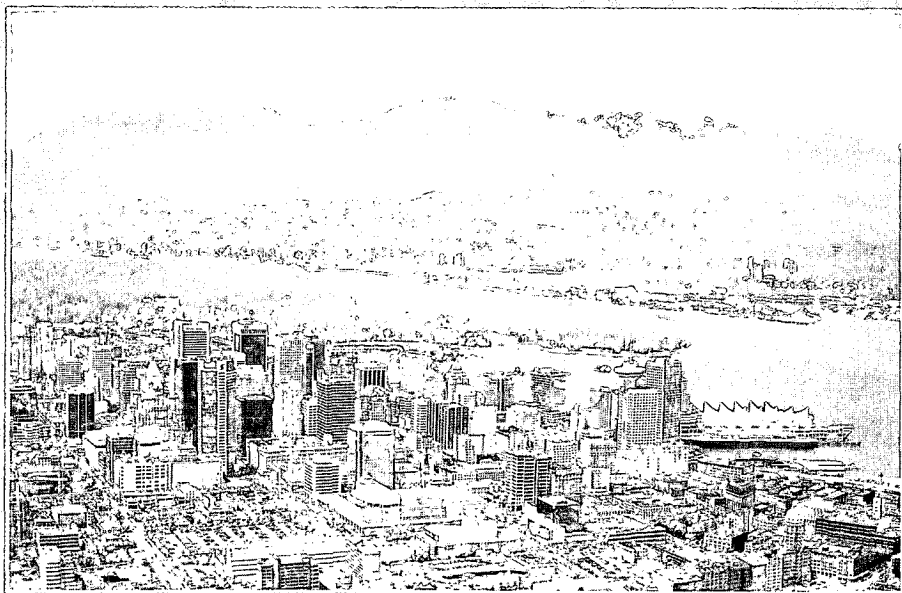
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# IN VITRO FERTILIZATION AND ASSISTED REPRODUCTION

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# The measurement of uterine blood flow impedance using the color Doppler sonogram does not help predict lower pregnancy rate (PRs) in women having appropriate endometrial thickness and echo patterns prior to oocyte retrieval

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## SUMMARY

This study used color Doppler imaging on day of oocyte retrieval to measure pulsatility index (PI) and resistance index (RI) to see if conception was associated with PI or RI values in 160 patients who underwent in vitro fertilization-embryo transfer. The women were  $\leq 40$  years old, had normal thickness and echo patterns on day of human chorionic gonadotropin, and had at least 2 embryos transferred. The comparison of mean PI and RI by conception outcome (125 did not conceive, 35 (28%) had clinical pregnancy)

showed no significant differences in mean PI ( $2.5 \pm .44$  vs  $2.6 \pm .44$ ) or RI ( $.87 \pm .04$  vs  $.88 \pm .04$ ). There were no pregnancies achieved when PI  $> 3.37$ , or RI  $> .945$ ; however, the number of cases was small (2 and 6, respectively). Doppler parameters of uterine blood impedance on day of oocyte retrieval did not correlate with conception in patients with adequate endometrial lining.

## INTRODUCTION

Uterine environment and receptivity play a major role in the successful implantation of embryos following in vitro fertilization-embryo transfer (IVF-ET). Early studies of uterine environment have focused on endometrial development assessed by sonographic measurements of endometrial thickness and echo pattern. These studies have found that thin endometria ( $< 10\text{mm}$ ) and endometria that have a hyperechogenic homogeneous echo pattern at time of peak follicular maturation are associated with reduced pregnancy rates (PRs) following IVF-ET (Check et al, 1991). More recently with the increased use of color Doppler imaging (CDI) with pulsed Doppler (PD), studies of the uterine environment have focused on measures of uterine blood flow impedance as assessed by the pulsatility index (PI) and resistance index (RI) of the uterine arteries (Cacciatore et al, 1996; Coulam et al, 1994; Steer et al, 1992; Serafini et al, 1994; Bassil et al, 1995). Some studies have concluded that low resistive flow patterns are important factors indicating adequate perfusion of the uterus and endometrial lining and correlate with success of implantation in IVF-ET.

These results have led to the question of whether or not uterine blood flow and endometrial development are inter-related, i.e., do women who develop normal endometria, i.e., thickness  $\geq 10\text{mm}$  and a tri-laminar pattern at time of human chorionic gonadotropin (hCG) injection have adequate uterine blood flow or could they still fail to conceive because of high impedance to the uterine blood flow. The objective of the current study was to assess the association of uterine blood flow as measured by PI and RI and outcome of IVF-ET in women with normal endometrial thickness and echo pattern.

## MATERIALS AND METHODS

A prospective observational study was conducted in which women undergoing IVF-ET between 9/1/95 and 8/31/96 at the Cooper Institute for IVF were eligible to enroll. Inclusion criteria were: 1) woman's age at time of IVF cycle was 40 years old or younger; 2) ovarian stimulation prior to oocyte retrieval; 3) no concomitant medications that could effect blood flow such as heparin or aspirin were taken; 4) sonographic measurements of the endometrium on day of hCG demonstrated an endometrial thickness  $\geq 10\text{mm}$  and a tri-laminar pattern. 160 women met these criteria in the time period noted. Only one cycle/patient was included in the study to assure independence of the observations.

All women had received ovarian stimulation following one of three protocols. 94 used the luteal phase leuprolide acetate/human menopausal gonadotropin (LA/hMG) protocol; 56 used the flare protocol (follicular phase LA in conjunction with hMG) and 10 were stimulated using a combination of clomiphene citrate (CC) and hMG without the use of any LA.

Frequent sonographic monitoring of follicular development was

conducted from the fifth day of gonadotropin stimulation. When at least two follicles attained a diameter of 18mm in conjunction with a serum estradiol ( $E_2$ ) level of at least 800pg/mL, 10,000 IU of hCG was administered. Endometrial thickness was measured in millimeters by placing calipers on the outer wall of the endometrium as seen in the longitudinal axis of the uterine body. Echo patterns were classified as tri-laminar (triple line or isoechogetic) or homogeneous hyperechogetic. Women who demonstrated adequate endometrial development at this time, i.e., had thickness of at least 10mm and a tri-laminar pattern were scheduled to have Doppler imaging performed on day of oocyte retrieval.

One hour prior to oocyte retrieval sonographic endometrial assessment (thickness and echo pattern) and Doppler examinations were performed using a 5 MHz endovaginal probe with color and PD capabilities (GE Logic 400, General Electric Medical Systems, Milwaukee, WI). The spatial peak average intensity was  $<75$  mW/cm<sup>2</sup> which is within the safety limits recommended by the Food and Drug Administration as well as the Bioeffects Committee of the American Institute of Ultrasound in Medicine. The wall filters were set at  $\leq 5$  cm/sec (depending on velocity scale) to eliminate low frequency signals occurring from noise. Color Doppler signals were obtained from the right and left ascending branches of the uterine arteries lateral to the cervix. A PD range gate was then placed over each artery to obtain flow velocity waveforms. Measurements of the PI and RI were obtained electronically by tracing the waveform and applying the following equations:  $PI = (A-B)/\text{mean FD}$  and  $RI = (A-B)/A$ , where A is the maximum systolic velocity, B is the end diastolic velocity and FD is frequency shift. Recordings of each artery were considered satisfactory when multiple consecutive waveforms of equal intensity were obtained. All endometrial grading and calculations of the PI and RI were performed by one sonographer to eliminate inter-rater variability. The sonographer was blinded to the nature of the study.

The main outcome measure was clinical pregnancy, i.e., sonographic confirmation of a gestational sac in the uterus. The average PI and RI of the two uterine arteries was computed and used in the statistical analysis. The mean PI and RI were compared by stimulation protocol using analysis of variance. Ovarian stimulation factors such as number of oocytes retrieved, fertilization rate and number of embryos transferred were compared by conception outcome using independent t-tests. The mean PI and RI levels were compared by conception outcome using t-tests. A p value of .05 was used.

## RESULTS AND CONCLUSIONS

Following ovarian stimulation, the mean uterine parameters measured did not differ by stimulation protocol so all women were combined into one group for further analysis.

Following ET, 35 (28%) clinical pregnancies were established. There was no difference in the mean number of oocytes retrieved, fertilization rates or number of embryos transferred by conception outcome.

The average PI of the two arteries ranged from 1.45 to 4.33 in the non-conception cycles (median 2.57) and from 1.69 to 3.37 in the conception cycles (median 2.51). There was no difference in the mean PI in conception (mean  $2.5 \pm .44$ ) cycles versus non-conception cycle (mean  $2.6 \pm .44$ ). There were no pregnancies achieved when the PI was  $>3.37$ , however there were only 2 women who demonstrated levels above this value.

The average RI of the two arteries ranged from .74 to .93 in the conception cycle (median .88) and from .74 to .97 in the non-conception cycles (median .89). There was no difference in the mean RI in conception (mean  $.87 \pm .04$ ) cycles versus non-conception cycle (mean  $.88 \pm .04$ ). There were no pregnancies achieved when the RI was  $>.94$ , however there were only 6 women who demonstrated levels above this value.

Despite advances in ovarian stimulation and embryo culture, the PRs following IVF-ET have remained around the 20% mark for many years (SART reports) (1996). The lack of improvement in PRs have led researchers to focus on the factors that occur beginning with ET. These include methods of ET, immunologic considerations, embryo quality, and uterine receptivity as measured by endometrial development and uterine blood flow.

In our study, we have tried to limit the effects of embryo quality by only including in our study younger women (at most 40 years old) who had at least 2 embryos transferred. All ETs were done using the same catheter and transfer procedure. Similarly, we have controlled for the effects of endometrial development by including only women who demonstrated an endometrium of at least 10mm with a tri-laminar pattern on the day of hCG. This study was thus able to address the issue of the relationship of uterine blood flow and conception outcome.

The results demonstrate that in the population studied, uterine blood impedance measured on day of oocyte retrieval does not relate to conception outcome. The occurrence of high impedance, by either high PI scores ( $>3.37$ ) or high RI scores (.94) are rare in patients achieving a normal mid-cycle endometrial thickness and echo pattern thus questioning the cost effectiveness of additional screening for poor uterine blood flow with CDI in this group.

This study, however has not considered all the possible information that CDI can provide the clinician in evaluating a patient who failed to conceive following ET. Further study is needed to evaluate the uterine blood flow in women with poorly developed endometria to see if the retarded development of the endometrium is related to poor uterine blood flow. It would be of interest to see if a greater percentage of high impedance is found in women with either decreased endometrial thickness or homogeneous hyperechogenic echo pattern at mid-cycle. Furthermore, such a study would evaluate if patients with normal blood flow, but inadequate thickness or abnormal echo pattern may still have PRs comparable to those with normal parameters.

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