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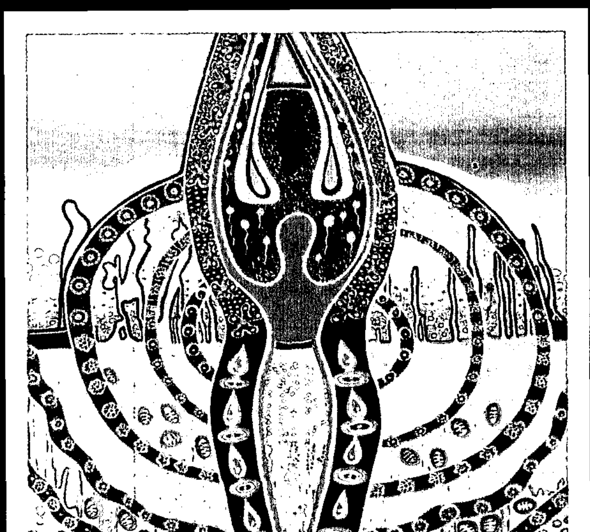

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Preliminary Evidence that Ovarian Stimulation in IVF-ET Cycles May Lower Vascular Impedance of the Uterine Arteries

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Summary

A study was conducted to determine if ovarian stimulation for oocyte retrieval had any effect on vascular impedance of the uterine arteries. Vascular impedance as measured by the pulsatility (PI) and resistance indices (RI) was compared in retrieval cycles using luteal phase leuprolide acetate/gonadotropin therapy to frozen embryo transfer cycles where oral estradiol was used for hormonal replacement. The PI was lower at mid-cycle in the stimulated cycles and both the PI and RI were lower in the luteal phase of the stimulated cycles; no difference was seen on day 2. Ovarian stimulation may lower vascular impedance and any decisions based on these values should consider the stimulation protocol utilized.

Introduction

Uterine environment and receptivity play a major role in the successful implantation of embryos following in vitro fertilization-embryo transfer (IVF-ET). More recently, studies have focused on measures of vascular impedance of the uterine arteries, obtained by color Doppler imaging to measure pulsatility (PI) and resistance indices (RI), to predict outcome. It has been reported that increased resistance to uterine blood flow negatively correlates with successful outcome in oocyte retrieval cycles (1-7). The reported maximum PI value considered to be optimal ranges from 3.0 (1-

4) to 3.3 (5,6). The same variation has also been reported with respect to the RI (3,7). This has not been corroborated by other studies (8). Ovarian stimulation has been demonstrated to reduce impedance to uterine blood flow when compared to natural cycles (5,9). It was observed in our center that women using oral estradiol in preparation for frozen ET had higher vascular impedance indices than women who had undergone ovarian stimulation for oocyte recovery and subsequent ET. The objective of this study was to investigate this observation and to determine if there is, indeed, any difference in vascular impedance in stimulated versus hormone replacement cycles.

Materials and Methods

A retrospective review of a series of oocyte retrieval and frozen ET cycles was conducted. All retrieval cycles (n=91) in which the stimulation protocol was the luteal phase leuprolide acetate followed by gonadotropin therapy were reviewed as well as all frozen ET cycles (n=103) where hormone replacement therapy using graduated dosages of oral estradiol was prescribed. Progesterone (P) support was used in the luteal phase of all cycles. All women were 38 years of age or younger. To be included in the study, measurements of the PI and RI had to be performed at three different times during the cycle: 1) baseline - day when down-regulation was achieved in retrieval cycles or day 2 of frozen ET cycles, 2) mid-cycle - day of human chorionic gonadotropin administration in retrieval cycles or day in which P therapy was commenced in frozen cycles, and 3) mid-luteal phase - 3 days post-ET. The age of the women undergoing ovarian stimulation ranged from 24 to 38 years with an average of 33.1$\pm$3.4 years. The women undergoing frozen ET ranged in age from 24 to 38 years with an average age of 32.3$\pm$3.8 years.

Sonographic assessment was performed using a multi-frequency endovaginal probe with color and pulsed Doppler capabilities (GE Logic 400, General Electric Medical Systems, Milwaukee, WI, USA). The spatial peak average intensity was $<$75 mW/cm2, which is within the safety limits recommended by the US Food and Drug administration as well as the Bioeffects Committee of the American Institute of Ultrasound. The wall filters were set at $\leq$5 cm/sec (depending on the velocity scale) to eliminate low frequency signals occurring from noise. Color Doppler signals were obtained from the ascending branches of the right and left uterine arteries at the level of the internal os. A pulsed Doppler range gate was then placed over each artery to obtain velocity waveforms. Recordings of each artery were considered satisfactory when multiple consecutive waveforms of equal intensity were obtained. Measurement of the PI and RI were obtained electronically by tracing the waveform and applying the equations: PI = (A-B)/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. All calculations were performed by one sonographer.

The main outcome measures were PI and RI at the three phases of the menstrual cycle. Analysis of variance was used to compare the changes in the indices throughout the cycle by stimulation. Post-hoc tests were performed when the main effects or interaction were significant. A p value of .05 was considered significant.

Results

There was a significant interaction effect between stimulation used and phase of the cycle (Table 1). In oocyte retrieval cycles with ovarian stimulation the mean baseline PI was 2.64±.71. This level was similar to the mean mid-cycle PI of 2.55±.50. However, the mean mid-luteal phase PI was significantly lower, 2.23±.49. In the frozen ET cycles baseline PI was similar to stimulated cycles (2.80±.75) and remained the same at mid-cycle (2.92±1.1), but did not decrease in the luteal phase (3.0±.68). Post-hoc testing comparing the stimulated to the frozen ET cycles demonstrated similar baseline levels but lower mid-cycle and luteal phase levels in the stimulated cycles. RI levels acted similarly, i.e., the levels did not differ throughout the unstimulated cycle, but decreased in the luteal phase of the retrieval cycles (mean RI levels - frozen ET cycles: .89±.06, .89±.05, .90±.04; retrieval cycles: .89±.05, .88±.05, .83±.06). Post-hoc testing demonstrated similar baseline and mid-cycle levels but lower luteal phase levels in the stimulated cycles.

Table 1: Comparison of vascular impedance indices by phase of cycle and stimulation (Data presented as mean ± standard deviation)

	Baseline	Mid-cycle	Mid-luteal
Stimulated cycles (n=91)			
PI	2.64 ±.71	2.55 ±.50	2.23 ±.49*
RI	.89 ±.05	.88 ±.05	.83 ±.06*
Frozen ETs (n=103)			
PI	2.80 ±.75	2.92 ±1.10	3.00 ±.68**
RI	.89 ±.06	.89 ±.05	.90 ±.04**

*p<.05, comparing luteal phase levels to other phases of cycle, ANOVA and post-hoc tests

**p=NS, comparing luteal phase levels to other phases of the cycle, ANOVA and post-hoc tests

Conclusions

Ovarian stimulation may lead to lower vascular impedance levels than those found in unstimulated frozen ET cycles, Decisions based on vascular impedance indices must consider the stimulation protocol utilized.

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