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A Study to Determine if Certain Sonographic Uterine Parameters Are Associated with Multiple Gestation

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Key Words
Multiple birth · Vascular impedance · Color Doppler · Resistance and pulsatility index

Abstract
The objective was to determine if lower uterine artery vascular impedance is associated with a greater likelihood of multiple gestation. Color Doppler parameters of pulsatility index, resistance index, endometrial thickness and echo patterns were measured in oocyte/retrieval cycles on days of human chorionic gonadotropin injection, oocyte retrieval, and mid-luteal phase in cycles where at least 3 embryos were transferred. Comparisons of these parameters were made in patients with single versus multiple gestations. There was no association between uterine environment as measured by vascular impedance and endometrial thickness and number of embryos implanted. Thus, a more ideal uterine environment, at least as determined by these sonographic parameters, does not seem to facilitate multiple embryo implantations.

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Introduction

Pregnancy rates (PRs) have been steadily increasing through improvement in in vitro fertilization-embryo transfer (IVF-ET) techniques. The downside to this success has been the increase in multiple birth rates. The fetal, neonatal and perinatal mortality rates have been shown to be 3–6 times higher in twin gestations as compared to singleton, and up to 15 times higher in triplet pregnancies [1]. Given the increase cost and risk involved with these births, many studies have been undertaken to attempt to determine how to lower the multiple birth rate. Many of these studies have focused strictly on limiting the number of embryos transferred [1–10]. Some studies have investigated restricting the number of embryos transferred based on the age of the patient and prior obstetrical history [11, 12]. Others have considered age and number of embryos along with other parameters such as duration of infertility, prior IVF attempts and number of oocytes fertilized [13, 14]. Additional parameters of embryo quality [15, 16] and/or embryo scoring [17–19] have also been considered.

The objective of this study was to determine if there was any association between uterine environment and

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multiple birth. Specifically, we compared the vascular impedance of the uterine arteries as measured by color Doppler imaging and endometrial thickness in women who had a single versus those with multiple gestations. To control for the number of embryos transferred, we considered only cycles in which at least 3 embryos were transferred.

Materials and Methods

A retrospective review was performed to identify all pregnancies conceived between January 1, 1997 and May 31, 1998 that resulted from ETs in which at least 3 embryos were transferred. By controlling for the number of embryos transferred, the study could focus on uterine environment.

Patients had undergone oocyte retrieval following ovarian stimulation with either the luteal phase leuprolide acetate (LA)/gonadotropin protocol or follicular phase LA/gonadotropins. All ETs were performed 3 days after oocyte retrieval. Embryo transfer was canceled if the endometrial thickness was < 8 mm and/or the endometrial echo pattern was homogeneous hyperechogenic (HH) on the day of human chorionic gonadotropin (hCG) injection. These embryos were then cryopreserved and ET was deferred to a subsequent hormone replacement cycle.

The patients were classified into two groups by the number of gestations achieved: single sac (n = 103) and multiple sacs (n = 66). The groups were compared to see if there were any differences in the measurements of vascular impedance to the uterine arteries by pulsatility index (PI), resistance index (RI), endometrial thickness, and echo pattern. These parameters were measured on the day of hCG and the day of oocyte retrieval.

Color Doppler imaging was performed using a multi-frequency endovaginal probe with color and pulsed Doppler capabilities (GE Logic 400, General Electric Medical Systems, Milwaukee, Wisc., USA). Color Doppler signals were obtained from the right and left ascending branches of the uterine arteries at the level of the internal os. A pulsed Doppler range gate was placed on each uterine artery to obtain velocity waveforms. Measurements of the PI and RI were obtained by electronically tracing the waveform and applying the following 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 the frequency shift.

Recordings of each artery were considered satisfactory when multiple consecutive waveforms were obtained. The average of the right and left arteries was used in the analysis. All calculations were performed by one sonographer.

Endometrial thickness was measured in millimeters by placing electronic calipers on the outer walls of the endometrium in the longitudinal axis of the uterine body. The endometrial echo patterns visualized sonographically were graded as triple-line (TL), isoechogenic (IE) and HH. All endometrial grading was performed by the same sonographer.

The outcome groups were also compared by stimulation characteristics, age, sera hormonal levels, and embryo quality. Statistical analysis included χ^2 analysis and independent t-test as indicated. A p value of 0.05 was used to determine significance.

Table 1. Comparison of stimulation characteristics by pregnancy type

	Single gestation (n = 103)	Multiple gestation (n = 66)
Age of patients, years	34.6 ± 4.5	35.1 ± 4.4
Stimulation		
Luteal phase LA	67 (65.0%)	38 (57.6%)
Follicular phase LA	36 (35.0)	28 (42.4%)
Oocytes retrieved	13.4 ± 7.3	12.7 ± 6.7
Fertilization rates	62.4 ± 20.8	65.9 ± 17.8
ICSI used	38.8%	37.9%
Assisted hatching used	95.1%	92.4%
Deselection used	45.6%	50.0%
Sera hormone levels		
Day of hCG		
Estradiol, pg/ml	2,200.0 ± 902.5	2,028.5 ± 872.9
Progesterone, ng/ml	1.0 ± 0.8	0.8 ± 0.5
Luteal phase		
Estradiol	1,254.6 ± 1,055.2	799.1 ± 688.5
Progesterone	96.2 ± 36.6	100.4 ± 71.2

Results

There was no difference in the average age of the patient achieving singleton pregnancies (34.6 ± 4.5 years) and those achieving multiple gestations (35.1 ± 4.4). The stimulation characteristics in both groups are summarized in table 1. There was no difference in the number of oocytes retrieved, fertilization rates, sera hormone levels throughout the cycle, stimulation protocol used, or the use of intracytoplasmic sperm injection, assisted hatching or embryo deselection in the two groups.

The number of embryos transferred was the same in both groups (table 2). When embryo quality was compared by fragmentation and blastomere shape there was no difference by group. However, when compared by cell stages, the group with multiple gestations had a larger percentage of embryos with more than 6 cells transferred than the singletons ($p < 0.05$) (table 2). The average cumulative embryo score, based on fragmentation and number of blastomeres per embryo, was the same in the two groups (70.2 ± 21.9 for singletons, 75.3 ± 19.7 for multiples) (table 2).

The average PI and RI levels were the same in both groups on the day of hCG, the day of oocyte retrieval and in the early luteal phase (table 3). The average endometrial thickness was the same in both groups at the 3 times of the cycle it was measured (table 3). The distribution of

Table 2. Comparison of embryos transferred by pregnancy type

	Single gestation	Multiple gestations
Embryos transferred	3.7 ± 0.90	3.7 ± 1.0
Embryo quality		
Fragmentation		
A = No fragmentation	57 (15.0%)	23 (9.0%)
B = < 25% fragmentation	282 (74.2%)	194 (80.5%)
C = 26–50% fragmentation	31 (8.2%)	18 (7.5%)
D = > 50% fragmentation	10 (2.6%)	6 (2.5%)
Shape		
1 = Even-sized round cells	131 (34.5%)	84 (35.3%)
2 = Slightly uneven-sized round cells	196 (51.6%)	132 (55.5%)
3 = Uneven-sized or irregularly shaped	53 (13.9%)	22 (9.2%)
Cell stages*		
< 4 cells	20 (5.3%)	7 (2.9%)
4–6 cells	165 (43.4%)	79 (33.2%)
7–9 cells	185 (48.7%)	150 (63.0%)
> 9 cells	10 (2.6%)	2 (0.8%)
Cumulative embryo score	70.2 ± 21.9	75.6 ± 19.7

* $p < 0.05$.

Table 3. A comparison of uterine parameters by pregnancy type

	Single gestation	Multiple gestations	
PI			
Day of hCG	2.63 ± 0.52	2.51 ± 0.52	
Day of retrieval	2.77 ± 0.58	2.67 ± 0.54	p = NS
Luteal phase	2.35 ± 0.59	2.26 ± 0.52	
RI			
Day of hCG	0.88 ± 0.04	0.88 ± 0.05	
Day of retrieval	0.87 ± 0.04	0.86 ± 0.04	p = NS
Luteal phase	0.85 ± 0.06	0.84 ± 0.04	
Endometrial thickness			
Day of hCG	11.18 ± 2.28	11.47 ± 2.19	
Day of retrieval	11.37 ± 2.12	11.47 ± 2.33	p = NS
Luteal phase	11.43 ± 2.20	11.93 ± 2.33	
Endometrial echo pattern			
Day of hCG			
TL	82.7%	86.2%	
IE	17.3%	13.8%	
Day of oocyte retrieval			
TL	77.1%	76.9%	
IE	19.9%	21.2%	
HH	3.1%	1.9%	
Luteal phase*			
TL	6.4%	9.1%	
IE	20.2%	41.8%	
HH	73.4%	49.1%	

* $p < 0.05$.

echo patterns was similar on the day of hCG and on the day of retrieval but differed in the two groups in the luteal phase (table 3).

Of the 103 singleton pregnancies, 82 (70.6%) delivered. There were 16 fetal demises, 4 spontaneous abortions, and 1 therapeutic abortion. Of the 66 multiple pregnancies, 34 delivered all gestations, 22 delivered some of the sacs, and 10 delivered none (5 spontaneous abortions, 4 fetal demises, and 1 therapeutic abortion). Thus, 82.1% of the women with multiple gestations had a successful delivery; 111 of the 156 (71.1%) fetuses successfully delivered.

Discussion

Some studies have focused on the uterine environment to determine the number of embryos to be transferred. One study used measurements of uterine blood flow impedance to determine uterine receptivity [20]. Another used the combination of parameters, i.e., endometrial thickness, vascular impedance, the appearance of the protodiastolic notch, and number of embryos transferred, to adopt a scoring system [21]. Each of these studies suggested transferring fewer embryos when the uterine environment appears most receptive. The studies also presented the multiple birth rates, but did not compare parameters between singleton and multiple gestations. There was no association between uterine environment as measured by vascular impedance and endometrial thickness and/or echo patterns and number of embryos implanted in the study presented herein. Thus, a more ideal uterine environment, at least as determined by these sonographic parameters, does not seem to facilitate multiple embryo implantations.

Previous data from our IVF center failed to show improved pregnancy or implantation rates according to embryo morphology or fragmentation [22]. The study presented herein further demonstrated that less fragmented embryos are not more likely to cause multiple gestations than more fragmented ones. Similar conclusions were reached by evaluating symmetry. However, embryo cell number did correlate with higher rates of multiple births suggesting that embryo factors rather than uterine environment has the greatest influence for multiple gestation [22].

The differences in mid-luteal echo patterns between the two groups needs to be confirmed with additional studies. Unfortunately, if these data are corroborated, it would not provide a practical method to help the clinician to decide on how many embryos to transfer since these measurements are obtained 3 days after transfer. These data are difficult to interpret in light of some recent data that a non-HH pattern 3 days after transfer may correlate with a decreased implantation and PR yet the present study suggests that if conception occurs it may result in a higher rate of multiple gestations [23].

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