

# Correlation between Perifollicular Vascularity and Outcome in Stimulated Intrauterine Insemination Treatment Cycles: A Study Using Two-Dimensional Transvaginal Power Doppler Ultrasound

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## Abstract

**Objective:** The aim of this study is to assess any potential relationship between perifollicular vascularity and occurrence of pregnancy in cases of stimulated IUI cycles using the subjective grading system by 2D transvaginal power Doppler ultrasonography. **Design:** A prospective cross sectional cohort study. **Method:** This is a prospective cross-sectional cohort study of 90 stimulated IUI treatment cycles. Selected women were prescribed clomiphene citrate combined with highly purified urinary follicle stimulating hormone. All patients underwent serial transvaginal ultrasound scans starting from day 6 to 7 of the cycle. Perifollicular Doppler blood flows were assessed in dominant follicles  $\geq 18$  mm. The patients then were categorized into 3 groups (high vascularity group {G3 & G4}, low vascularity group {G1 & G2} and mixed grades group). Other parameters measured included number of follicles  $\geq 18$  mm in both ovaries, endometrial thickness and estradiol ( $E_2$ ) level. Human chorionic gonadotropin (hCG) injection 10,000 IU IM was given to the patient when the dominant follicle reached 18 mm in diameter. At that time, the endometrium was evaluated as regards endometrial thickness. IUI was carried out using prepared/"washed" semen (husband). All patients received luteal support in the form of progesterone from day of IUI for 14 days. Serum B-hCG was estimated 2 weeks after insemination. **Results:** In this study, from all 90 cases only 8 cases got pregnant with pregnancy rate of 8.88% (6 cases got pregnant in high grade vascularity group; 2 cases in mixed grades group and no cases got pregnant in low grade group). There was statistically significant difference among the 3 groups as regarding the pregnancy rate (P value = 0.02). There is statistically significant difference in perifollicular resistance index (RI) and pulsa-

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tility index (PI) between pregnant and non pregnant cases (P value = 0.016 and 0.047 respectively). In this study, there is no statistically significant difference between pregnant and non pregnant cases as regarding endometrial thickness and E<sub>2</sub> level at the day of hCG administration (P value = 0.39 and 0.76 respectively). Conclusion: Perifollicular blood-flow assessment by 2D transvaginal power Doppler is a good predictive for the outcome of stimulated IUI cycles.

## Keywords

Perifollicular Vascularity, IUI, 2D Power Doppler Ultrasound

## 1. Introduction

Intrauterine insemination (IUI) has long been established as an alternative to other forms of assisted reproductive techniques (ART). The use of gonadotrophins in IUI has been shown to improve significantly the pregnancy rate. However, the risk of both ovarian hyperstimulation syndrome and multiple pregnancies is significantly increased. Despite this, IUI has cost savings and is less invasive compared with other forms of ART in particular for non-tubal infertility [1].

There are intense angiogenesis and increased capillary permeability during follicular development, ovulation and subsequent formation of the corpus luteum. Neovascularization is an important phenomenon for the growth and selection of ovulatory follicles as well as for the subsequent development and function of the corpus luteum. Studies of ovarian vasculature showed that the capillary network of preovulatory follicles was more extensive than that of other follicles. Therefore, initiation and maintenance of follicular growth depend on development of the follicular microvasculature [2].

The growing oocyte is provided with a developmental milieu like the intrafollicular level of oxygen and vascular endothelial growth factor (VEGF) that play a crucial role in the health of the developing oocyte. The vascularity of the parent follicle from which the oocyte is retrieved during IVF is known to influence the viability of the embryo [3].

With the development of power Doppler imaging, the pattern of perifollicular perfusion can be determined accurately. Transvaginal color flow Doppler has been used in several studies to assess uterine and ovarian blood flow patterns in ART cycles [4]-[7]. The blood flow in the wall of the preovulatory follicle can be used to assess the quality of the oocyte and to predict the potential success of ART cycles [4]. Greater blood flow in the wall of the preovulatory follicle has been associated with improved pregnancy rates of IUI [5] and *in vitro* fertilization (IVF) and embryo transfer [4]. Follicular blood-flow assessment by transvaginal color flow Doppler has been used during oocyte retrieval for selection of oocytes with better development as the vascularity tended to be greater for preovulatory follicles that contained a mature oocyte [7].

The aim of this study is to assess any potential relationship between perifollicular vascularity and occurrence of pregnancy in cases of stimulated IUI cycles using the subjective grading system by transvaginal Doppler ultrasonography.

## 2. Patients and Method

This is a prospective cross-sectional cohort study of 90 stimulated IUI treatment cycles carried out at Assisted Reproduction Unit in Zagazig University Hospital. This study was performed between January 2012 and January 2013.

Normogonadotropic women aged 20 - 38 years; with normal ovarian reserves, no previous surgeries on the ovary/ovaries, no tubal factor and of unexplained infertility were included in the study. We excluded women with endometriosis, polycystic ovarian disease, prior surgery, single ovary, severe male factor infertility and poor ovarian reserves.

The following was done for all selected patients: full history; full clinical examination; tubal patency test in the form of hysterosalpingogram or laparoscopy; semen analysis; and basal pelvic ultrasound scan to exclude pelvic pathology such as ovarian cysts before starting ovarian stimulation.

Women were prescribed clomiphene citrate (clomid tablets, 50 mg, Aventis Co., Cairo) administered orally,

starting on the second day of the menstrual cycle for 5 consecutive days combined with highly purified urinary follicle stimulating hormone (fostimon vial, IBSA Co., Cairo) containing urofollitrophin 75 IU in the form of intramuscular injection.

All patients underwent serial transvaginal ultrasound scans starting from day 6 to 7 of the cycle and continued every alternate day until human chorionic gonadotropin (hCG) was administered using transvaginal ultrasound scan with power and color Doppler facilities (Medison Co. Accuvix V20, 7.5 MHz, South Korea). The size of the follicle was calculated by using the mean of two maximum diameters. Perifollicular Doppler blood flows were assessed in dominant follicles  $\geq 18$  mm. We placed the power Doppler color over each ovarian follicle and then took a cross-sectional image of the follicle with the maximum color intensity representing the greatest Doppler frequency shifts. The follicular circumference was frozen and the perifollicular blood flow (PFBF) was graded based on Chui *et al.* [8]. According to this modified grading system, ovarian PFBF was represented as: Grade 0: 0%, Grade 1: 1% - 25%, Grade 2: 26% - 50%, Grade 3: 51% - 75%, Grade 4: 76% - 100%. The flow velocity waveforms from the ovarian stromal or intra-ovarian arteries of both the ovaries were obtained in order to calculate the resistance index (RI), pulsatility index (PI) and systolic/diastolic ratio (S/D). A recording was considered satisfactory for measurement when there were three intense waveforms in a row and an average of each index in both ovaries was calculated. The patients then were categorized into 3 groups (high vascularity group {G3 & G4}, low vascularity group {G1 & G2} and Mixed grades group). Others parameters measured included number of follicles  $\geq 18$  mm in both ovaries, endometrial thickness and estradiol level. Human chorionic gonadotropin injection 10,000 IU IM (Pregnyl Ampoule 5000 IU, Nile Co., Cairo) was given to the patient when the dominant follicle reached 18 mm in diameter. At that time, the endometrium was evaluated as regards endometrial thickness. IUI was carried out using prepared/"washed" semen (husband). All patients received luteal support in the form of progesterone from day of IUI for 14 days. Serum B-hCG was estimated 2 weeks after insemination.

Statistical analysis was performed using STATA 11.0 (College Station, Texas, USA). Data were presented as a number (%) or mean  $\pm$  standard deviation (SD)/median (range). The differences in Mean/Median values were measured by using Student's t-test (normal data distribution)/Wilcoxon Ranksum Test (for categorical variables). The correlation between outcome measures and perifollicular blood flow were calculated using Spearman rank correlation.  $P < 0.05$  was considered to be statistically significant.

The study was approved by Zagazig University Medical Research Council Laboratories Joint Ethics Committee. All participants signed an informed consent. Rigorous confidentiality was maintained.

### 3. Results

**Table 1** shows the demographic features of the studied patients. There is no statistically significant difference between the three groups as regarding age, body mass index (BMI) and type, duration and cause of infertility. There is no statistically significant difference in perifollicular PI and RI between the three groups ( $P$  value = 0.83 and 0.32 respectively). There is no statistically significant difference between the three groups as regarding number of days from starting stimulation till day of HCG administration, diameter of follicles and endometrial thickness. There is no statistically significant difference between the three groups as regarding number of follicles and  $E_2$  level at the day of hCG administration ( $P$  value  $< 0.0001$  and 0.018 respectively).

In this study, from all 90 cases only 8 cases got pregnant with pregnancy rate of 8.88% (6 cases got pregnant in high grade vascularity group; 2 cases in mixed grades group and no cases got pregnant in low grade group). There was statistically significant difference between the 3 groups as regarding the pregnancy rate ( $P$  value = 0.02). There is statistically significant difference in perifollicular RI and PI between pregnant and non pregnant cases ( $P$  value = 0.016 and 0.047 respectively). In this study, there is no statistically significant difference between pregnant and non pregnant cases as regarding endometrial thickness and  $E_2$  level at the day of hCG administration ( $P$  value = 0.39 and 0.76 respectively) (**Tables 2-4**).

### 4. Discussion

A relationship between ovarian vascularity and chances of pregnancy has been reported since the early 1990s, but debate remains regarding the entity of this association and its clinical value [9]. In this study, from all 90 cases only 8 cases got pregnant with pregnancy rate 8.88% (6 cases got pregnant in high grade vascularity

**Table 1.** Demographic data of the patients.

	High grade		Mixed grade		Low grade		F	P value
Age (year)								
Mean ± SD	27.9 ± 4.9		28.5 ± 4.1		27.3 ± 4.5		0.62	0.53
Range	21 - 38		20 - 35		20 - 35			
BMI								
Mean ± SD	26.7 ± 2.1		26.7 ± 2.4		26.6 ± 2.2		0.01	0.98
Range	22.6 - 30		23 - 30		22 - 30			
Type of infer	n	%	n	%	n	%		
Primary	17	56.7	15	50	19	63.3	1.09	0.58
Secondary	13	43.3	15	50	11	36.7		
Duration of infer								
Mean ± SD	3.4 ± 2.1		3.36 ± 1.7		3.7 ± 2.2		0.24	0.78
Range	1 - 8		1 - 8		1 - 8			
Cause of infer	n	%	n	%	n	%		
Unexplained	15	50	15	50	15	50	0.22	0.99
Male factor	5	16.7	4	13.3	4	13.3		
Female factor	10	33.3	11	36.7	11	36.7		

**Table 2.** Data on stimulation regime, ovarian and endocrine response of the patients.

	High grade	Mixed grade	Low grade	F	P value
No. of days from starting stimulation to HCG administration					
Mean ± SD	13.5 ± 1.7	13.6 ± 1.4	14.16 ± 1.97	1.44	0.24
Range	9 - 17	10 - 16	10 - 19		
No of follicles					
Mean ± SD	1.3 ± 0.7	2.2 ± 0.4	1.53 ± 0.7	17.3	<0.0001*
Range	1 - 4	2 - 3	1 - 4		
Diameter of follicles					
Mean ± SD	20.1 ± 1.5	19.7 ± 1.2	19.7 ± 1.2	0.62	0.53
Range	18 - 23	18 - 23	18 - 23		
PI					
Mean ± SD	0.9 ± 0.08	0.91 ± 0.08	0.9 ± 0.07	0.18	0.83
Range	0.8 - 1.09	0.81 - 1.09	0.83 - 1.09		
RI					
Mean ± SD	0.496 ± 0.07	0.48 ± 0.04	0.5 ± 0.05	1.13	0.32
Range	0.43 - 0.67	0.43 - 0.58	0.43 - 0.6		
ET					
Mean ± SD	9.2 ± 1.26	9.76 ± 1.1	9.5 ± 1.3	1.6	0.1
Range	7.6 - 13	7.6 - 12	8 - 12		
E2 level					
Mean ± SD	521.8 ± 106	607.1 ± 106*	573 ± 130.2	4.18	0.018*
range	401 - 879	490 - 927	412 - 987		
Day of IUI					
Mean ± SD	14.4 ± 1.9	14.5 ± 1.6	15.2 ± 2.2	0.74	0.48
Range	11 - 18	12 - 17	11 - 20		

**Table 3.** Pregnancy rates among the studied groups.

	High grade		Mixed grade		Low grade		F	P value
Pregnancy	n	%	N	%	N	%		
Negative	24	80	28	93.3	30*	100	(7.68)*	(0.02)*
Positive	6	20	2	6.7	(0)*	(0)		

**Table 4.** Data on patient characteristics, stimulation regime and ovarian and endocrine response of pregnant and non pregnant cases.

	-VE n = 82		+VE n = 8		T	P value
Age (year)						
Mean $\pm$ SD	28 $\pm$ 4.6		26.8 $\pm$ 3.7		0.81	0.4
Range	20 - 38		22 - 34			
BMI						
Mean $\pm$ SD	26.7 $\pm$ 2.2		27.1 $\pm$ 2.3		0.57	0.56
Range	22 - 30		23.6 - 30			
Duration of infer						
Mean $\pm$ SD	3.37 $\pm$ 2		4.4 $\pm$ 1.9		1.5	0.13
Range	1 - 8		2 - 7			
Cause of infer	n	%	n	%		
Unexplained	44	53.68	1	12.5	4.57	0.1
Male factor	11	12.32	2	25		
Female factor	27	33.8	5	62.5		
Type of infertility	n	%	n	%		
Primary	46	57.5	5	50	0.01	0.9
Secondary	34	42.5	5	50		
No. of follicles						
Mean $\pm$ SD	1.7 $\pm$ 0.7		1.5 $\pm$ 0.7		0.9	0.36
Range	1 - 4		1 - 3			
Diam. of follicles						
Mean $\pm$ SD	19.7 $\pm$ 1.3		20.3 $\pm$ 1.3		1.14	0.25
Range	18 - 23		18 - 23			
PI						
Mean $\pm$ SD	0.91 $\pm$ 0.08		0.847 $\pm$ 0.03		2.43	0.016*
Range	0.8 - 1.09		0.8 - 0.9			
RI						
Mean $\pm$ SD	0.495 $\pm$ 0.05		0.46 $\pm$ 0.02		2.01	0.047*
Range	0.43 - 0.67		0.43 - 0.5			
ET						
Mean $\pm$ SD	9.4 $\pm$ 1.2		9.8 $\pm$ 1.06		0.85	0.39
Range	7.6 - 13		8.9 - 12			
E2 level						
Mean $\pm$ SD	568.7 $\pm$ 121.3		556.4 $\pm$ 102		0.3	0.76
Range	402 - 989		401 - 689			
IUI day						
Mean $\pm$ SD	14.7 $\pm$ 2		14.6 $\pm$ 1.1		0.12	0.9
Range	11 - 20		13 - 16			

group; 2 cases in mixed grades group and no cases got pregnant in low grade group). There was statistically significant difference between the 3 groups as regarding the pregnancy rate (P value = 0.02). There is statistically significant difference in perfollicular PI and RI between pregnant and non pregnant cases (P value = 0.016 and 0.047 respectively). This trend towards better peri-follicular vascularity in women who got pregnant was demonstrated in previous studies [9]-[14]. In a study of 182 consecutive patients undergoing stimulated IUI cycles, the incidence of follicles showing high-grade peri-follicular vascularity was reported to be associated with better outcome [10]. Shrestha *et al.* demonstrated an upward trend in the proportion of large follicles with high-grade peri-follicular blood flow along the follicular phase in cycles resulting in pregnancy [11]. However, Chui *et al.* failed to demonstrate any significant difference in the intra-ovarian PI between those women who conceived and those who did not [7].

The mechanism underlying the link between follicular vascularity and implantation outcome remains unclear at present. However, possibilities include a link between ovarian follicular blood flow and oocyte quality. The quality and maturity of the oocyte depends on the intrafollicular levels of oxygen which in turn is directly proportional to the degree of follicular vascularity. Hence, PFBF may be used as a valid indirect marker of oocyte

quality [12]. An association between poor follicular vascularity and aneuploidy has been observed by a number of authors [13] [14]. Chui *et al.* demonstrated that oocytes derived from follicles with low grade vascularity resulted in a significantly higher proportion of triploid embryos when compared to those derived from follicles with high grade vascularity [8]. Similarly, Bhal *et al.* showed a significantly higher oocyte retrieval rate, maturity and fertilization rate with significantly lower triploidy rate in the group with high grade vascularized follicles [15]. The compromised perifollicular microcirculation leads to hypoxia which probably causes an increased incidence of aneuploidal oocytes. However, the question remains unanswered whether the hCG trigger injection used to induce ovulation alters the pattern of PFBF by the time oocyte recovery is performed. It has been demonstrated that the exogenous hCG or endogenous luteinizing hormone surge increases angiogenesis of human ovarian follicles by increasing the local angiogenic factor VEGF production [14].

In this study, there is no statistically significant difference between pregnant and non pregnant cases as regarding endometrial thickness (P value = 0.39). Chien *et al.* studied the effect of endometrial thickness and pattern measured using ultrasound upon pregnancy outcomes in patients undergoing IVF-ET. They assessed and recorded endometrial patterns and thickness on the day of hCG administration. They concluded that endometrial thickness and pattern independently affect pregnant outcomes [16]. Combined endometrial thickness and pattern could not predict the outcome of IVF-ET when endometrial thickness was <7 mm or >14 mm, while a triple-line pattern with a moderate endometrial thickness appeared to be associated with a good clinical outcome [17].

In this study, there is no statistically significant difference between pregnant and non pregnant cases as regarding E<sub>2</sub> level at the day of hCG administration (P value = 0.76). High E<sub>2</sub> levels have been shown to affect embryonic adhesion, while a negative association between the probability of pregnancy and E<sub>2</sub> levels on the day of hCG has been reported [18]. On the other hand, several studies have suggested that pregnancy achievement is independent of E<sub>2</sub> levels on the day of hCG administration [19].

An adequate blood supply remains fundamental in the regulation of intrafollicular oxygen levels and the determination of oocyte quality. We performed this study using 2D power Doppler which has its own limitations. The information regarding the vascularization and blood flow is derived from a single artery, which may not be the true representative of the surrounding vasculature or total ovarian blood flow [20]. Furthermore, the accuracy of measurement of blood flow velocity is dependent on the angle of insonation to the blood vessels. This may at times be difficult to measure correctly as the arteries within the ovary are not only small but tortuous also [21]. Our study was designed prospectively using 2D color and power Doppler technology. The door is open to larger studies using 3D Doppler technology to be performed in order to substantiate our results. Three dimensional power Doppler is essentially more sensitive, angle independent and evaluates the total vascularization and blood flow of the ovary [22].

## 5. Conclusion

Perifollicular blood-flow assessment by 2D transvaginal power Doppler ultrasonography is a good predictive for the outcome of stimulated IUI cycles.

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## Disclosure of Interests

None.

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