The Predictive Power of Follicular Resistance Index (RI) And Peak Systolic Velocity (PSV) In Optimizing Conception Outcomes: A Quantitative Approach to Fertility Assessment

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| Keywords	Abstract
	Background: Assisted reproductive techniques (ART) deals with complex aspects of fertility, with the help of advanced ultrasonography. If the follicular vascular indices are not in the defined range, it means that the follicle is not yet physiologically mature and, therefore, stimulation still needs to be continued.
	Objective: To determine effective follicular RI and PSV for conception in IUI cycles measured on two dimensional (2D), power and colour doppler ultrasound.
	Material and methods: This prospective study included 231 women undergoing IUI treatment. Written informed consent for participation in the study was obtained from each patient.
	Results: It was observed that majority patients conceived when their follicular RI was between 0.4 to 0.5 and PSV>10 had conceived during their cycles.
	Conclusion: RI < 0.5 and PSV > 10 are very pertinent parameters for assessing the ovarian flow, as they correlate well with oocyte recovery rates and thus they play a very pivotal role in determining the most appropriate time to administer hCG.

INTRODUCTION

Assisted reproductive techniques (ART) deals with complex aspects of fertility, with the help of advanced ultrasonography. Complexities during conception occur in females due to continuous hormonal changes during their entire menstrual cycle. A thorough assessment of hormonal changes is essential, as uterus and ovaries undergo morphological and vascular changes during the menstrual phase. Growth, maturity and dominance of antral follicles is assessed in preovulatory scan.

A follicle that grows to 12 mm is a dominant follicle and it grows at a rate of 2 to 3 mm/day and ovulation occurs usually at 18 to 24 mm size. When the follicular size reaches up to 10 mm, follicular flow can be first detected[1] and its resistance starts falling 2 days prior to ovulation. A round follicle of 16 to 18 mm size (Fig 1), having thin walls with no internal echogenicities is a mature follicle.

On color doppler vascularity is seen surrounding 3/4th of the follicular circumference (Fig 1,3 and 4A). On pulse doppler these vessels show RI 0.4-0.48[2] and PSV > 10 cm/sec (Fig 2,3 and 4C). A sonolucent halo appears surrounding the follicle 24 hours prior to ovulation. Cumulus oophorus, a small projection from wall in the follicular lumen may be seen. (Fig 4B). If the follicular vascular indices are not in the defined range, it means that the follicle is not yet physiologically mature and, therefore, stimulation still needs to be continued.

The follicle is said to be functionally mature when PSV is 10 cm/sec, that is the time when the LH surge starts and under the effect of that LH, the perifollicular PSV keeps on rising constantly. Follicular blood flow velocity starts increasing approximately 26 to 29 hours before rupture and continues till 72 hours after rupture. Rising PSV with steady low RI suggests that the follicle is close to rupture.[1] Steady or decreasing PSV with rising RI suggests that the follicle is proceeding towards LUF.[3]
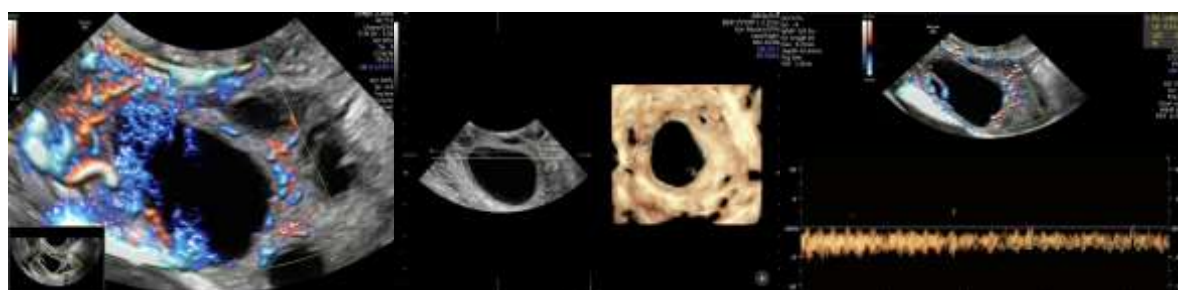
Fig. 1: Preovulatory follicle with 2D power Doppler
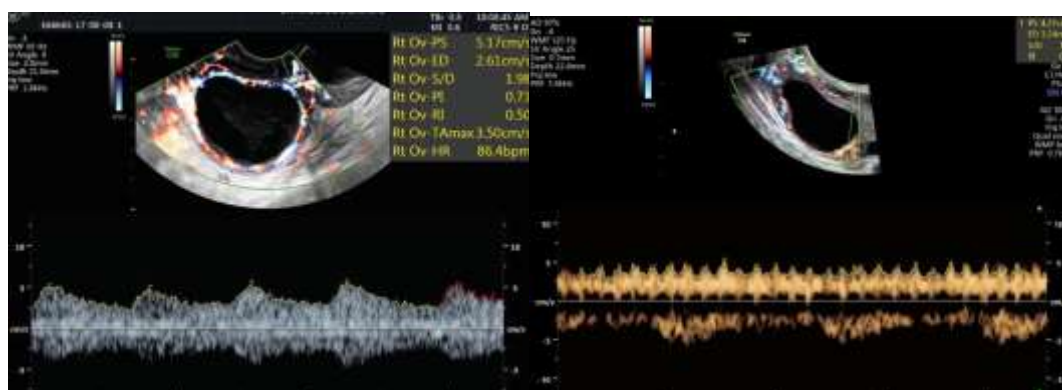
Fig. 2: Preovulatory follicle with pulse showing low Resistance

Fig. 3: Preovulatory follicle with vascular Doppler ring Surrounding the follicle and pulse flow Doppler waveform

Fig 4 A to C: (A) Perifollicular flow on Power doppler. (B)Cumulus, (C) Spectral Doppler of Perifollicular flow

OBJECTIVE

To determine effective follicular RI and PSV for conception in IUI cycles measured on two dimensional (2D), power and colour doppler ultrasound.

MATERIAL AND METHODS

This prospective study was conducted in India which included 231 women, undergoing IUI treatment. Written informed consent for participation in the study was obtained from each patient. Selection of women was carried on the basis of following inclusion and exclusion criteria.

Inclusion criteria

1. Infertile women having the age 22-45 years
2. Women undergoing fertility treatment
3. Mild adenomyosis not affecting the endometrial growth (with minimal endometrial growth up to 7 mm)
4. BMI < 30

Exclusion criteria

1. Women having infertility attributed to endocrinal abnormalities
2. Stage III and IV endometriosis
3. Known psychological disorders
4. Uterine pathologies (Fluid in endometrial cavity, polyp, fibroid)
5. Inadequate response of endometrial lining (endometrial thickness <7 mm)
6. Tubal factor infertility
7. Multifollicular development (> 3 Follicles of larger than 16cm)
8. Coagulation disorders

METHODOLOGY

Patient data including maternal age, height, weight, BMI, cause of infertility, previous history of IVF attempts and pregnancies was collected. On day 2, the patient was asked to empty her bladder and was undressed and placed in lithotomy like position on a gynecology couch after counseling, and a verbal consent was obtained from the patient. Transvaginal probe of frequency 5–9 mHz of Voluson E10 (GE Medical System, Kretz) was used for all scans. After assessment of the uterus, the scanning was continued for assessment of the ovaries. B mode assessment of the ovaries for measurement of ovarian diameters, volume, and counting of the antral follicles (diameter up to 9 mm) was done. Once ovaries were located, the probe was rotated to find out the longest diameter of the ovary and was stored as one frame on a dual screen. The probe was then rotated 90° anticlockwise to get a transverse section of the ovary (Fig. 5A and B). The ovarian volume can be calculated by the formula $X \times Y \times Z \times 0.523$ in milliliter. The antral follicles were counted in the whole ovary by taking a 2D sweep across the whole ovary and eyeballing.
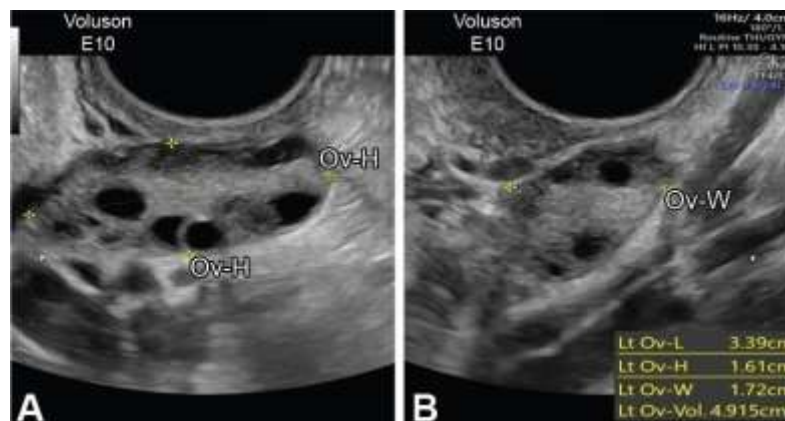
Figs 5A and B: Measurement of ovarian diameters in longitudinal and transverse section in 2D ultrasound

For assessment of ovarian stromal flow and to calculate resistance index (RI) and peak systolic velocity (PSV), the color Doppler PRF was set at 0.3 and wall motion filters (WMFs) at the lowest with optimal gains and balance setting. For pulse wave, the WMF was set at 30 Hz. The brightest vessel was selected for interrogation.

The gonadotropin dose was calculated based on the baseline scoring system devised by Panchal et al.[4] The doses according to the patient's score were decided, based on the study by Panchal et al. Gonadotropin was started on day 2 or day 3 of menstrual cycle.

Here, we have used recombinant follicle stimulating hormone (FSH) or highly purified urinary FSH. Either fixed or flexible protocol of antagonist was followed. In the fixed protocol, GnRH antagonist was started on day 6 of stimulation till the date of ovulation trigger.[5] In the flexible protocol, GnRH antagonist was started once the leading follicle is more than 14 mm.[6] Antagonist used was cetrorelix, 0.25 mg/day. The gonadotropin dosage was adjusted according to ovarian response. When three or more follicles greater than 18 mm in diameter were documented, Doppler was done to assess the flow to confirm functional maturity. Perifollicular vessels (vessels overlying the follicular wall) covering at least 2/3rd of the circumference of the follicle preferably 3/4th, with RI of 0.4–0.4815 and PSV >10 cm/second, were the desired parameters.

Statistical analysis

Women undergoing IUI, for treatment of infertility had quantitative and qualitative indices of follicular vascularity obtained on the day of hCG administration. Follicular RI and PSV was measured and quality of flow was graded amongst the largest follicles in both the ovaries. Mean RI and PSV of follicle were compared in women during their conception and non conception cycles using an unpaired Student's *t*-test. (Table 1)

		RI	PSV
Conception Cycle	*Mean*	0.458	11.720
	SD	0.082	4.246
	N	231	231
Non Conception Cycle			
	Mean	0.582	9.843
	SD	0.088	2.690
	N	231	231
	T value	15.668	5.676
	P value	<0.0001	<0.0001
		HS	HS

Table 1: Mean, Standard deviation, T value and P value of RI and PSV during conception   and non conception cycle

RESULTS

We have studied 231 women in present study. Transvaginal ultrasonography was done for the assessment of vascularity indices within the follicle. Patients were assessed in their conception and non conception cycles for follicular RI and PSV.

It was found that for conception mean RI value was 0.4576 and for non conception mean RI value was 0.58223. (Table 2) In the present study 231 patients were studied during their non conception and conception cycles during their treatment. Amongst 231 patients, 203 (87.9%) had RI of 0.5-0.6 and they could not conceive in their cycle whereas 137 (59.3%) patients had RI between 0.4-0.5 and they have conceived during their cycle. (Table 2-4; Graph 1-5)

|	N	Range	Mean	Std. Deviation
Non Conception Cycle RI	231	0.670	0.58223	0.087896
Non Conception Cycle PSV	231	17.7900	9.84300	2.690000
Conception Cycle RI	231	0.67	0.4576	0.082440
Conception Cycle PSV	231	40.1000	11.7200	4.2350401

Table 2 : Mean and Standard deviation of RI and PSV during conception and non conception cycle

Non Conception Cycle RI			
RI Value	Frequency	Percent	Cumulative Percent
.100 - .200	0	0.0	0.0
.200 - .300	0	0.0	0.0
.300 - .400	6	2.6	2.6
.400 - .500	22	9.5	12.1
.500 - .600	203	87.9	100.0
Total	231	100.0	

Table 3 : RI value during non conception cycle

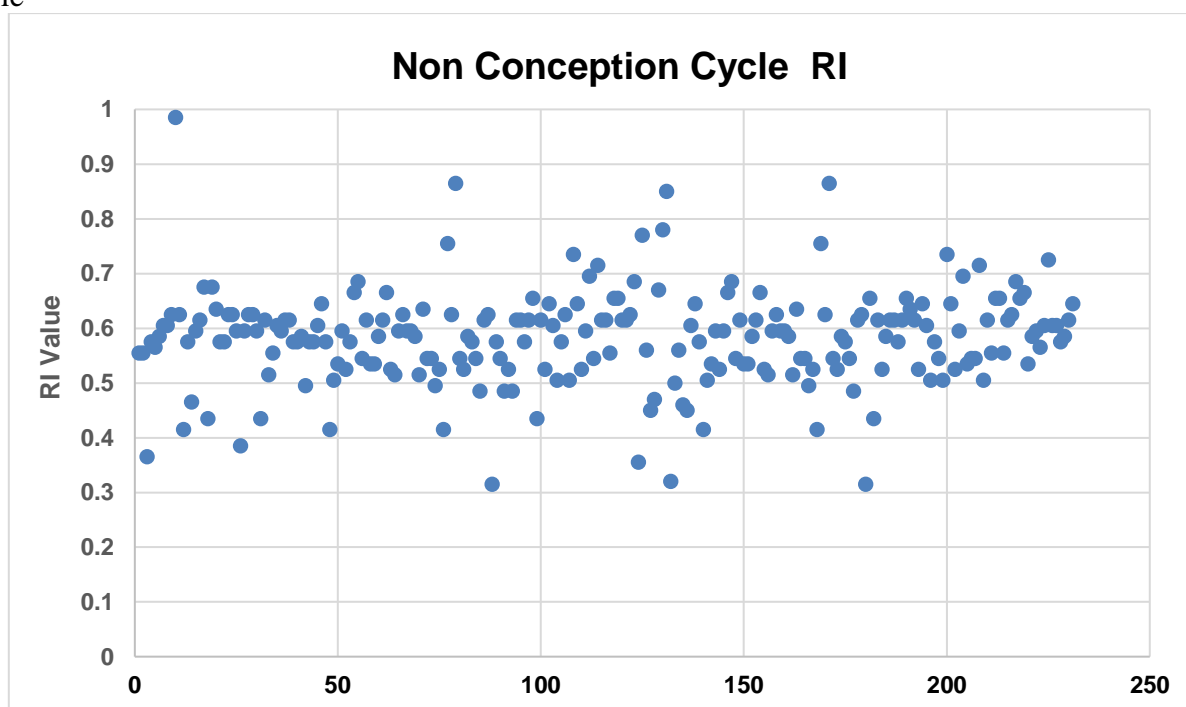| Conception Cycle RI			
RI Value	Frequency	Percent	Cumulative Percent
.100 - .200	2	0.9	0.9
.200 - .300	9	3.9	4.8
.300 - .400	39	16.9	21.6
.400 - .500	137	59.3	81.0
.500 - .600	44	19.0	100.0
Total	231	100.0	

Table 4 : RI value during conception cycle
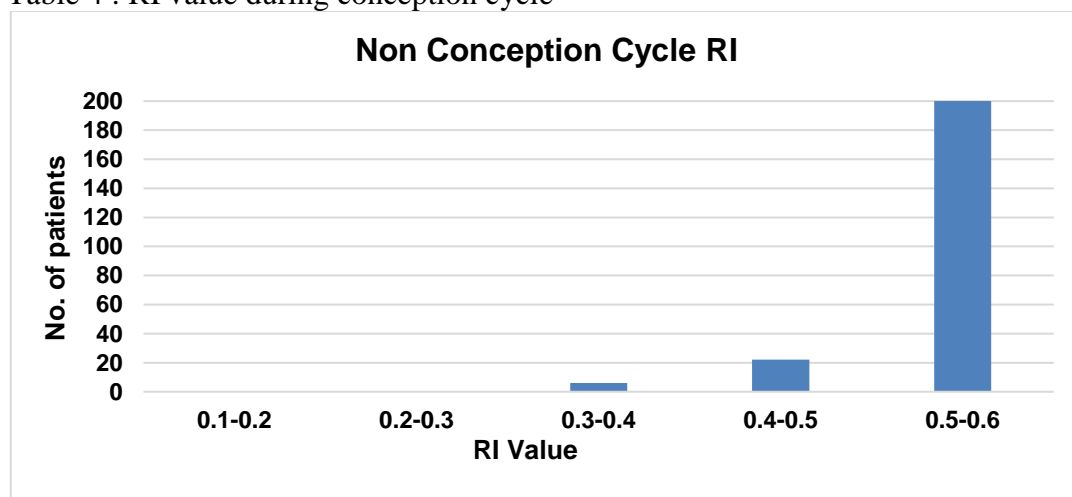
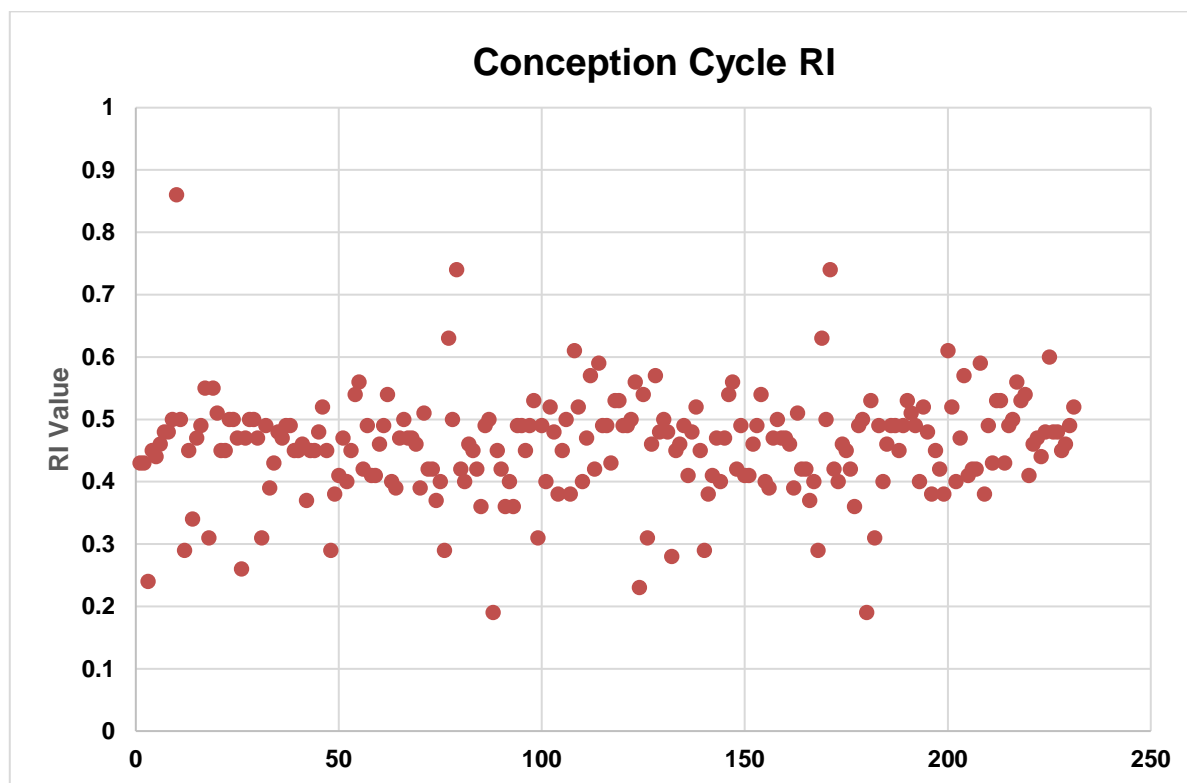Graph 1: Histogram showing relationship between RI and number of patients during non conception cycle
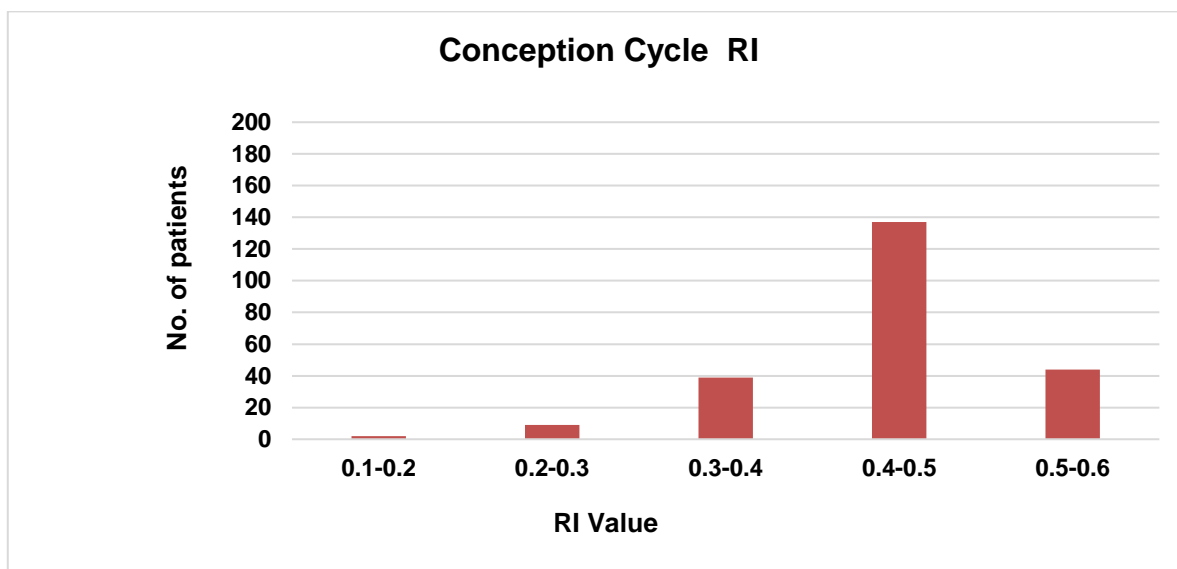
Graph 2: Histogram showing relationship between RI and number of patients during conception cycle
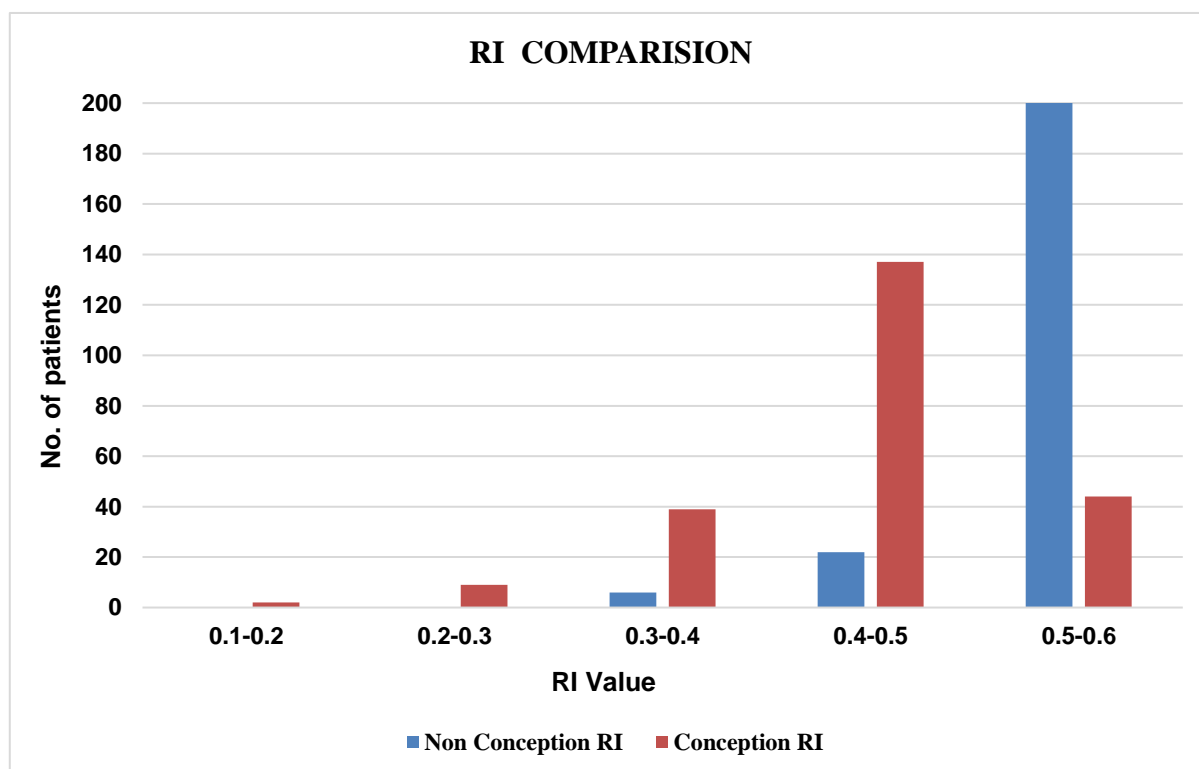

Graph 3: Scatterplot of Follicular RI and patients during their non conception cycles

Graph 4: Scatterplot of Follicular RI and patients during their conception cycles

Graph 5: Histogram showing comparison of RI values and number of patients between Conception and Non conception cycles

In the present study it was observed that majority patients conceived when their follicular RI was between 0.4 to 0.5.

It was found that for conception mean PSV value was 11.720 and for non conception mean

PSV value was 9.843. (Table 2) In the present study 231 patients were studied during their non conception and conception cycles during their treatment. Amongst 231 patients, 188 (81.4%) patients had PSV >10 and they have conceived during their cycle. (Table: 5,6; Graph: 6-10)

Non Conception Cycle PSV			
PSV	**Frequency**	**Percent**	**Cumulative Percent**
<2.5000	0	0.0	0.0
2.5001 - 5.0000	2	0.9	0.9
5.0001 - 7.5000	45	19.5	20.3
7.5001 - 10.0000	84	36.4	56.7
>10.0000	100	43.3	100.0
Total	231	100.0	

Table 5: PSV value during non conception cycle

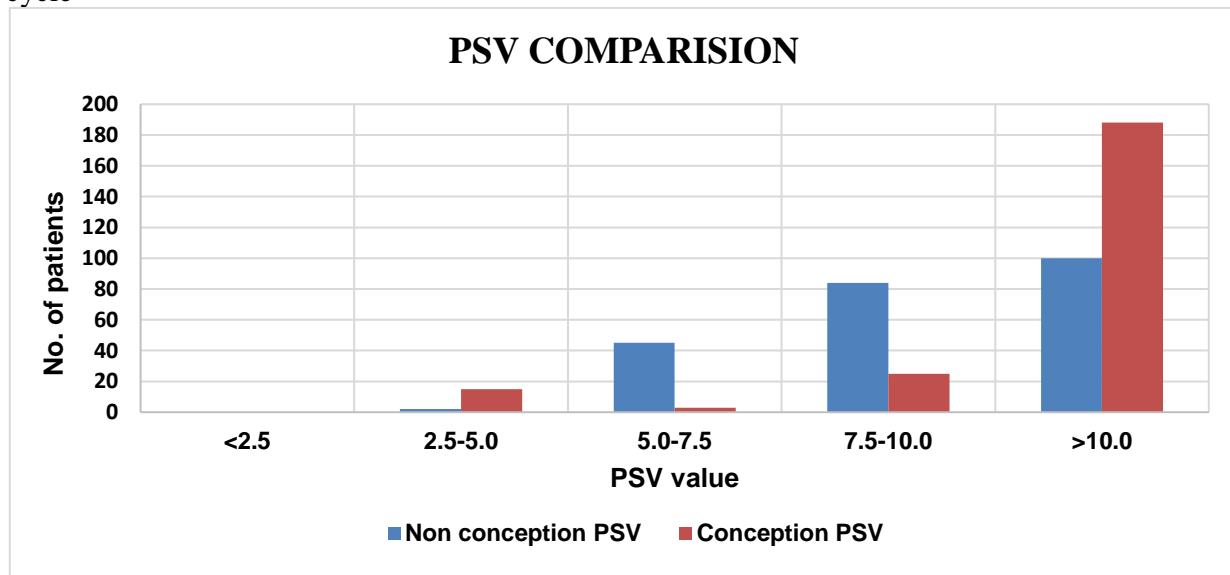| Conception Cycle PSV			
PSV	**Frequency**	**Percent**	**Cumulative Percent**
<2.5000	0	0.0	0.0
2.5001 - 5.0000	15	6.5	6.5
5.0001 - 7.5000	3	1.3	7.8
7.5001 - 10.0000	25	10.8	18.6
>10.0000	188	81.4	100.0
Total	231	100.0	

Table 6: PSV value during conception cycle
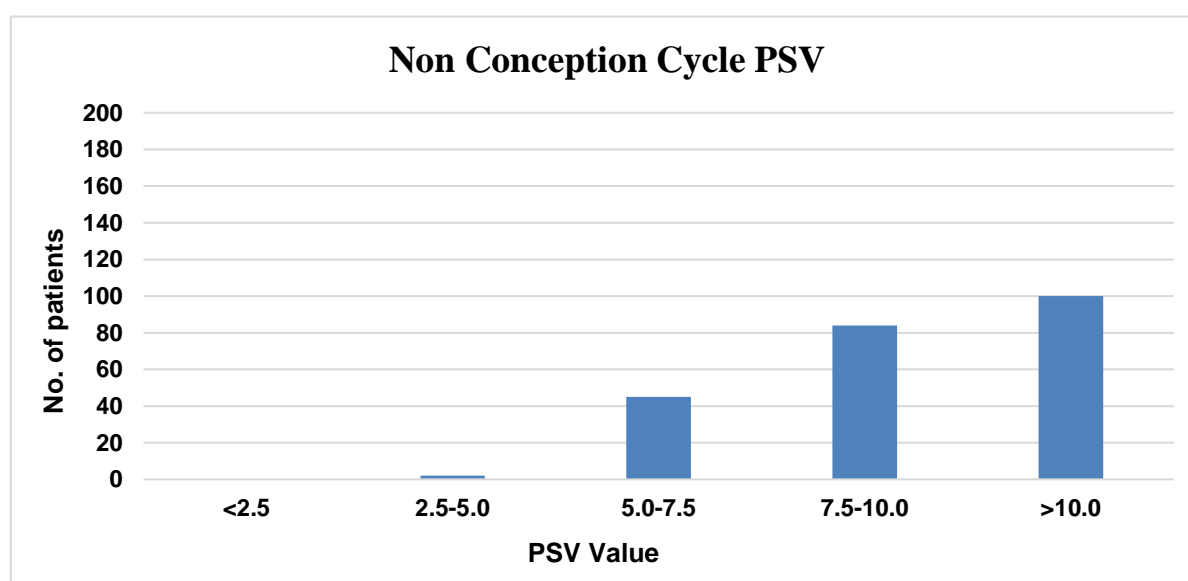
Graph 6: Histogram showing relationship between PSV and number of patients during non conception cycle
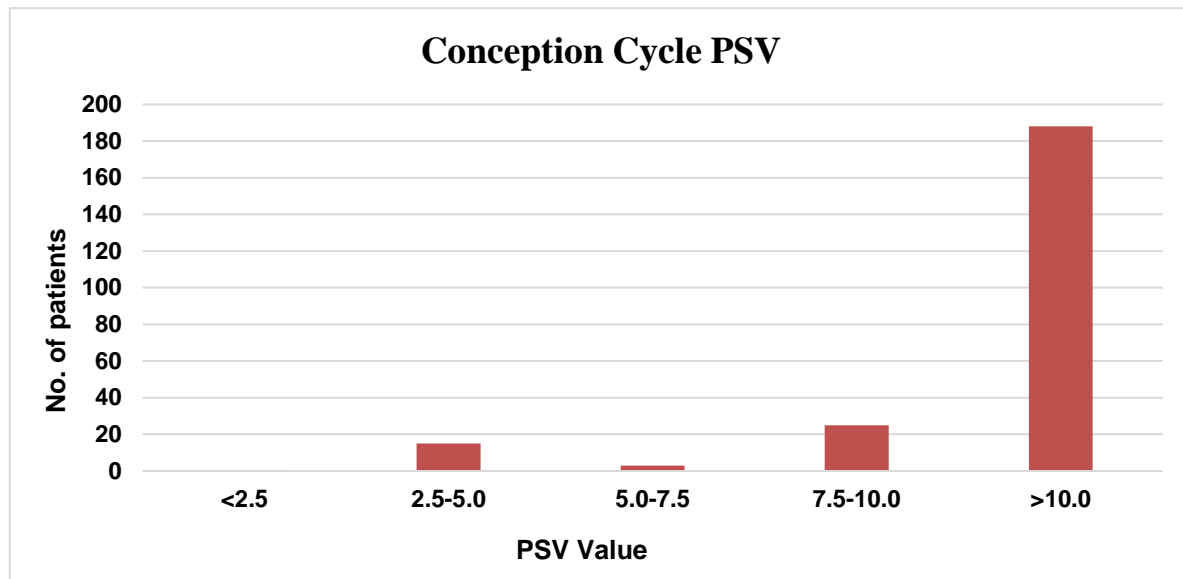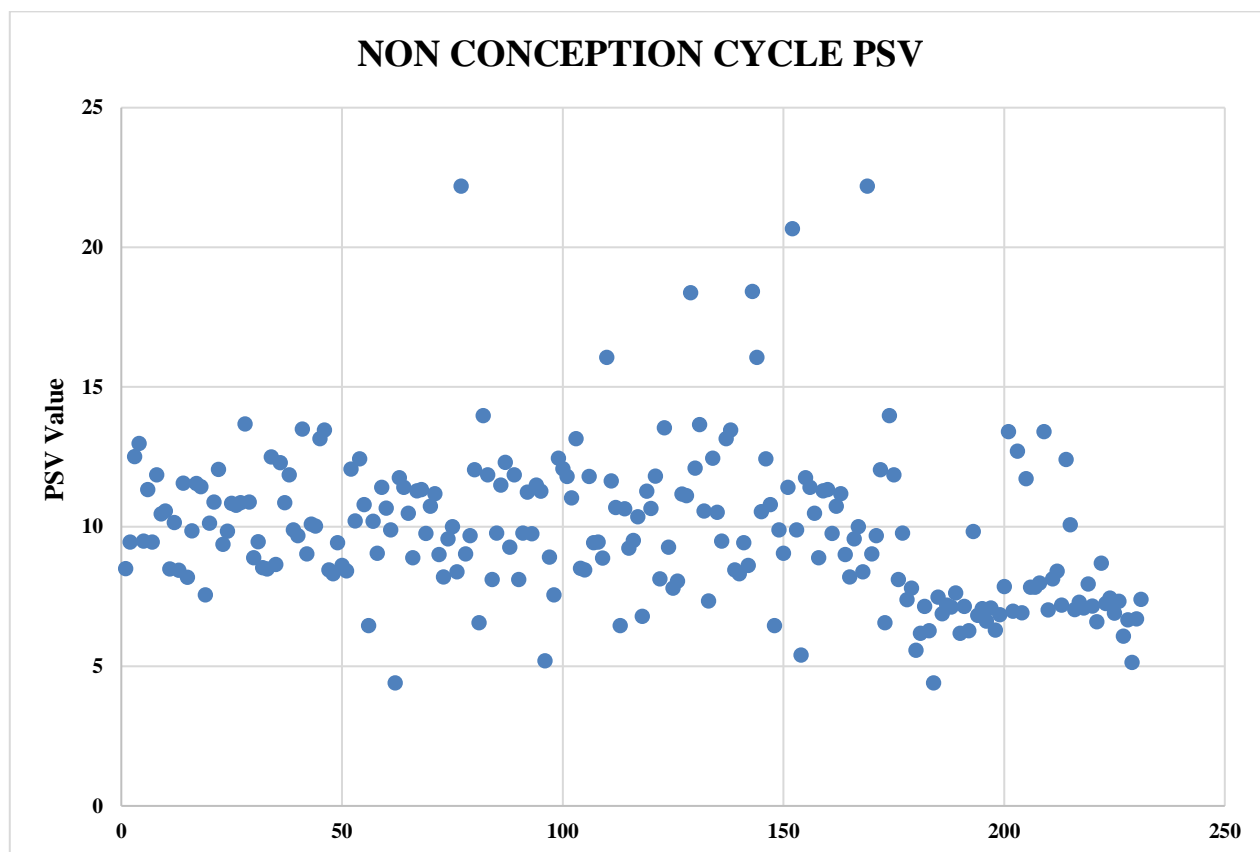
Graph 7: Histogram showing relationship between PSV and number of patients during conception cycle
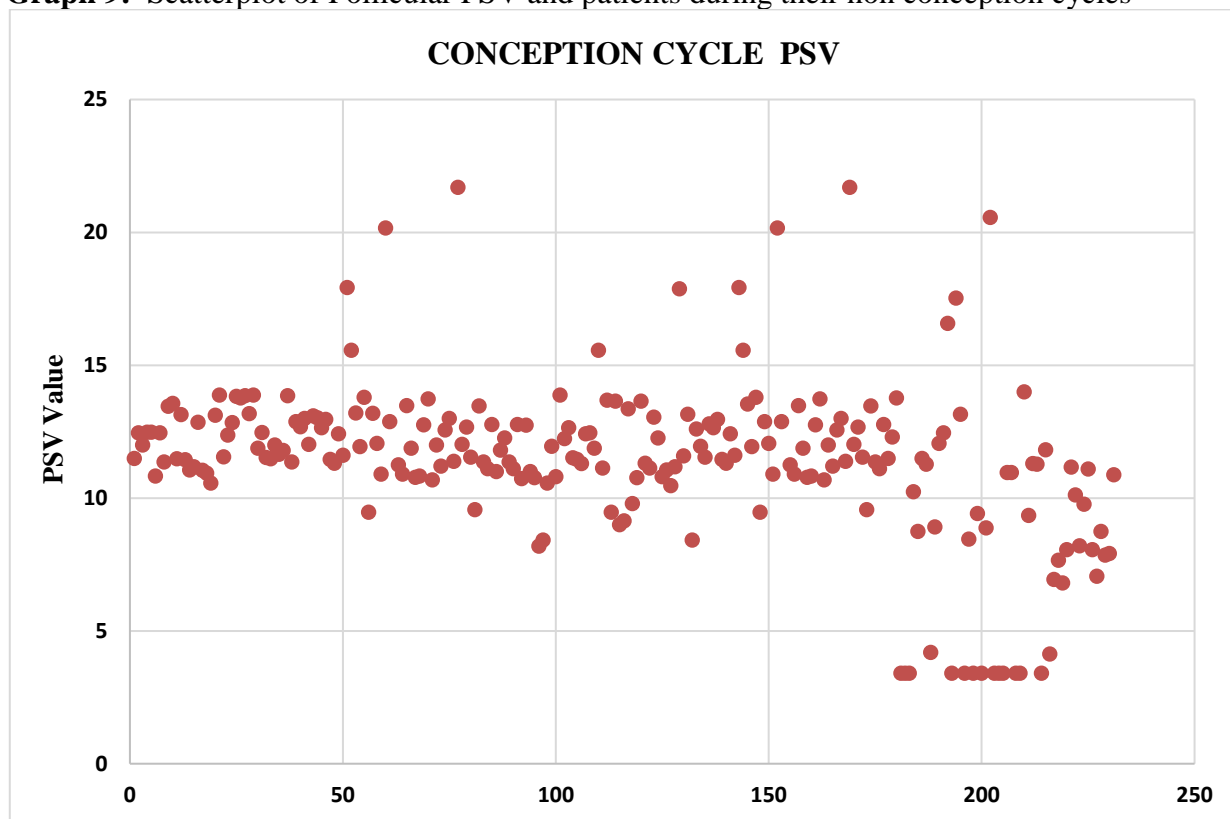

Graph 8: Histogram showing comparison of PSV values and number of patients between Conception and Non conception cycles

In our study we found that majority patients having follicular PSV>10 had conceived during their cycles.

Graph 9: Scatterplot of Follicular PSV and patients during their non conception cycles

Graph 10: Scatterplot of Follicular PSV and patients during their conception cycles

DISCUSSION

The aim of our study is to define the role of quantitative measurements of follicular blood flow in predicting and assessing their effectiveness in increasing the pregnancy outcomes. Our study included 231 women, they underwent transvaginal ultrasonography at our centre. It was done for the assessment of vascularity indices

within the follicle. Patients were assessed in their conception and non conception cycles for follicular RI and PSV. It was found that for conception mean RI value was 0.4576 and for non conception mean RI value was 0.58223. Amongst 231 patients, 203 (87.9%) had RI of 0.5-0.6 and they could not conceive in their cycle whereas 137 (59.3%) patients had RI between 0.4-0.5 and they have conceived during their cycle. We observed that majority patients conceived when their follicular RI was between 0.4 to 0.5. It was also found that for conception mean PSV value was 11.720 and for non conception mean RI value was 9.843. Amongst 231 patients, 188 (81.4%) patients had PSV >10 and they have conceived during their cycle. Majority patients conceived when their follicular PSV was >10. Similar results were observed by Panchal et al has shown that when the perifollicular RI is RI > 0.53 and PSV < 9 cm/sec, 12 hours before hCG injection, their conception rates were only 10.76 and 14.2%, respectively as compared with 32.8% and 28.2% respectively and individually when perifollicular RI <0.50 and PSV >11 cm/sec.[7]

Higher follicular RI and lower PSV indicates higher resistance flow to the follicle indicating reduced flow during diastolic phase and thus decrease in phasic oxygen to the ovum resulting in poor maturity of the follicle. It has been quoted in a study by Nargund et al[8,9] that embryos produced by fertilization of the ova obtained from the follicles, which had a perifollicular PSV of <10 cm/sec, are less likely to be grade I embryos and also have higher chance of chromosomal malformations. In the same study, it has been shown that the probability of developing a grade 1 or 2 embryo is 75%, if PSV was >10 cm/sec, 40% if PSV was <10 cm/sec, 24% if there was no perifollicular flow. There is yet another study that supports this finding. Oocytes from severely hypoxic follicles are associated with high frequency of abnormalities of organization of chromosomes on metaphase spindle and may lead to segregation disorders and catastrophic mosaics in embryo.[10]

PSV of individual follicles among women undergoing IVF has been shown to be correlated with oocyte recovery [8,9,11], fertilization rate [8], developmental potential of the oocyte [12] and quality of the preimplantation embryo [8,11,13]. A preliminary study [13] using qualitative assessment of follicular flow suggested that high-grade follicular vascularity is associated with increased pregnancy rate.

The relationship between pregnancy and qualitative grading of follicular vascularity has been confirmed by Coulam et al[14] and they included quantitative measurements of follicular blood flow also. In their study all pregnancies occurred in women with grade 3 and 4 follicular vascularity and 91% of pregnancies occurred with follicular PSV >10 cm/s. Women who had at least one follicle with a PSV of >10 cm/s at the time of hCG administration had a significantly higher pregnancy rate than women with maximum follicular PSV <10 cm/s. However, even in a population at high risk for IVF failure, women with follicular flow of PSV >10 cm/s and grade 3–4 had a 13% pregnancy rate in that cycle. This finding is consistent with previous studies [8,9] that reported a significant relationship between follicular PSV within a given follicle and the recovery of an oocyte and the subsequent production of an embryo. The probability of producing a high-grade embryo was 75% if the follicular PSV was >10 cm/s[9]

Follicle/oocyte determine the successful outcome of the pregnancy rather than their complete cohort. While it is true that the more follicles/oocytes available, the higher the probability that one of these will have the developmental potential to generate a viable pregnancy, it also holds true that if only one follicle possessing the developmental potential is available, the probability of pregnancy approaches 100%. The concept of quality rather than quantity is further emphasized when the number of follicles with grade 3–4 flow in an individual was compared to pregnancy rates during that cycle. The key is to be able to identify follicles that hold the potential to generate viable pregnancies.

Conclusion

Transvaginal ultrasound including 2D, power and pulse doppler much more accurate for follicular assessment. Their knowledge helps us to assess the overall vascularity of the follicle. RI < 0.5 and PSV > 10 are very pertinent parameters for assessing the ovarian flow, as they correlate well with oocyte recovery rates and thus they play a very pivotal role in determining the most appropriate time to administer hCG. Our study suggested that better follicular vascularity is associated with increased pregnancy rate.

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