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Role of perifollicular blood flow and 2-D Doppler indices on the day of HCG in predicting outcome of IUI Cycle

[1]Dr. Manisha Choudhary, Professor & HOD, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

[2]Dr. Vikas Chandra Swarankar, Assistant professor, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

[3]Dr. Jai Chowdhary, Associate Professor, Department of Radiology Mahatma Gandhi Medical College & Hospital, Jaipur.

[4]Dr. Sangita Sharma, Associate Professor, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

[5]Dr. Alka Gahlot, Professor, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

[6]Dr. Tatapudi S V Parvathi Devi, Mch Resident, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

[7]Dr. Sana Naqash, Mch Resident, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

Corresponding Author: Dr. Sangita Sharma, Associate Professor, Department of Reproductive Medicine & Surgery Mahatma Gandhi Medical College & Hospital, Jaipur.

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Abstract

Aim: To assess follicular maturity by 2D- power and color Doppler on the day of HCG to predict the outcome of IUI cycle.

Design: Prospective longitudinal study.

Materials and Methods: 150 stimulated IUI cycles carried out between may 2021 to April 2022 were taken for study. Selected patients, after complete workup were given letrozole 5 mg daily for 5 days from D3 of cycle with or without u- HMG added on D6 till HCG. On the basis of perifollicular blood flow (PFBF) assessment on the day of HCG by transvaginal 2D- power Doppler, patients were divided in 3 groups. Group-A consisted of patients with a PFBF of 76% to 100%, Group-B with a PFBF of 51% to 75% and Group-C with a PFBF of 0% to 50%. The flow velocity waveforms from perifollicular arteries were obtained in order to calculate the resistance index (RI) and peak systole volume (PSV). Other parameters measured were number of follicles > 18mm and endometrial thickness (ET) on the day of HCG. HCG 10,000 IU was given when dominant follicle >18mm and IUI was carried out 38-40 hours after HCG injection.

Luteal support was given in the form of progesterone from the day of IUI, for 14 days. Serum β HCG was estimated 2 weeks after IUI. Viable pregnancy was confirmed by sonography 2 weeks after β HCG.

Results: In this study 20 cases out of 150 (13.33%) got pregnant. Out of 20 cases 12 were from group-A (24%), 6 were from group –B (12%) and 2 were from group –C (4%). This difference in pregnancy rate was statistically significant (P- 0.0124) between the three groups. There is also a statistically significant difference in perifollicular RI and PSV value between three groups (P value 0.001).

Conclusion: Perifollicular blood flow (PFBF) assessment on the day of HCG by 2D transvaginal power Doppler is a good predictor for the outcome of stimulated IUI cycles.

Keywords: Perifollicular blood flow (PFBF), intrauterine insemination (IUI), 2D power Doppler ultrasound(2D-PD).

Introduction

Though IUI has not been included as ART procedure by most of the clinics but this is taken as a first line treatment in most of the cases of non-tubal infertility (1) like mild male factor, mild PCO, mild endometriosis as well as unexplained infertility. Super ovulation with IUI helps in conception by bypassing the cervical mucus barrier and increasing the gamete density, both oocytes and sperms at the site of fertilization (2). IUI is also a less invasive and less costly procedure for infertile couples with less visits and monitoring as well. The only drawback is its low success rate. With advancement in ultrasound technology, newer parameters have been developed to assess the maturity of oocyte before IUI, so as to assess the success rate of IUI cycle. Follicular maturity is a complex process dependent on multiple biochemical, morphological and vascular changes. It was already recognized as early as 1926, that neovascularization may be of prime importance in the growth and selection of ovulatory follicles in addition to the subsequent development and function of corpus luteum (3, 4)

Neovascularization depends on hormonal environment of follicle. It was also observed that the capillary network of preovulatory follicle was more extensive than that of other follicles, (5). Intense angiogenesis and increased capillary permeability in turns provide intrafollicular milieu in the form of oxygen, nutrients and different growth factors like VEGF for the maturity of oocyte. The perifollicular blood flow (PFBF) of preovulatory follicle (> 18m) reflects quality of the oocyte and helps to predict the potential success of ART cycle, as greater blood flow has been associated with improved pregnancy rates and low abortion rate. Assessment of perifolicular blood flow as a prognostic marker provides a safe, inexpensive and easy way to assess the quality of oocyte.

Transvaginal color Doppler has been used quite extensively to assess uterine and ovarian blood flow patterns in ART cycles since 1990's (6, 7, 8). The power Doppler has a threefold increase in sensitivity compared with conventional color Doppler imaging at detecting low velocity blood flow (9, 10). So power Doppler has a superior visualization in assessment of perifollicular vascularity (11, 12, 13).

Assessment of PFBF can be done in either qualitative or a quantitative way. Mostly used is the qualitative way to assess how much circumference of the follicle is covered by the blood vessels. The classification given by chui et al (12) is used for grading of PFBF as given in table – 1. The power Doppler indices taken for quantitative assessment include PI, RI and PSV of perifollicular arteries. The 3-D power Doppler can further assess the follicular volume, presence of cumulus and VI, FI and VFI of the follicle (14). Though 3-D power Doppler helps in assessing the global vascularity of follicle and gives a better idea about follicular maturity and therefore the quality of oocyte but there are issues of cost, availability and technical difficulty. So the aim of our study is to assess the pattern of PFBF with RI and PSV values on the day of HCG with the help of more convenient and easily available 2 D transvaginal power Doppler and to correlate it with pregnancy outcome in IUI cycles.

Table 1:

Grading system for the follicles vascularity, expressed in percentage of follicular circumference in which flow was identified (Chui et al 1997) (12)

F1	<25% of the follicular circumference
F2	25-50% of the follicular circumference
F3	51-75% of the follicular circumference
F4	>75% of the follicular circumference

Material and method

This is a prospective longitudinal study of 150 IUI cycles carried out in the department of Reproductive Medicine at mahatma Gandhi medical college and hospital. This study was performed between May 2021 to April 2022.

The women included were aged 20-35 years with normal ovarian reserve and hormone profile on day 3. Women having unexplained infertility of less than 5years, mild PCO and mild male factor were included in the study. Women having h/o ovarian surgery, endometriosis, single ovary, poor ovarian reserve, moderate to severe male factor, tubal factor of infertility and thin endometrium < 7mm on the day of HCG were excluded from the study. All women were evaluated by complete history, physical examination, TVS, semen analysis and required investigations to fulfill the criteria of inclusion. Tubal patency was checked by either HSG or hysterolapros copy according to patient profile.

After complete workup, the women included in study were asked to come on day 2 or 3 of cycle to start induction. Baseline TVS for AFC & FSH levels were checked. Women were prescribed, letrazole 5mg orally for 5 days with or without gonadotropins (u- HMG) in doses 75-150 iu according to age, ovarian reserve & BMI and continued till DF is > 18mm. The follicular monitoring was started on D10 and continued on every alternate day until HCG was administered, by transvaginal ultrasound with 2 D power & color Doppler (Siemens Acuson X300).

The size of the follicle was calculated by using the mean of two maximum diameters. Perifollicular blood flow (PFBF) was assessed by 2 D power Doppler of all follicles > 18mm. The power Doppler color was placed over each dominant follicle to see how much of the circumference of the follicle was covered by the blood vessels. All TVS studies were performed by single operator.

The pulse repetition frequency (PRF) was set at 3KHz, wall factor at the lowest, balance at 180 and gains just enough to fill up perifolicular vessels but not to spill the color outside the blood vessels. The vessels that overlap and obliterate the visibility of the follicular wall only were considered perifollicular vessels. The PFBF was graded in three groups based on chai et al (12). Group A consisted of patients with a PFBF of 76% to 100%, group B with a perifolicular blood flow of 51% to 75% and group C with a PFBF of 0% to 50%. Clinical pregnancy rates were compared in three groups. The flow velocity waveforms from perifollicular arteries were obtained in order to calculate the resistance index (RI) and peak systolic volume (PSV). Other parameters included were number of DF > 18mm and endometrial thickness. Human chorionic gonadotropin injection 10,000 IU i/m was given to the patients having DF > 18mm. IUI was carried out 38-40 hours after HCG. Semen sample was prepared by using density gradient method followed by swim up. All patients received luteal support in the form of micronized progesterone (oral or vaginal) from day of IUI for 14 days. Serum β-HCG was done 2 weeks after insemination. Viable pregnancy was confirmed by sonography 2 weeks after β-HCG positive report.

Statistical analysis

Chi - square and Anova test was carried out for statistical analysis. Results were expressed as mean and standard deviation of the mean. P- value < 0.05 was considered significant.

- The study was approved by ethical committee of mahatma Gandhi University. (Letter No. MGMCH/IEC/ JPR/ 2021/ 296, dated 12/ 3 /2021). All participants signed an informed consent. Complete confidentiality was maintained.

Results

In this study table -2 shows the demographic features of the studied patients in all three groups. There is no statistically significant difference between the three groups as regarding age of patients, BMI, duration and type of infertility. The cause of infertility including unexplained, male and female factors is also statistically non-significant in all three groups.

Table 2:

Demography	High Grade (50 Cases)		Mixed Grade (50 Cases)		Low Grade (50 Cases)		P Value
Age (Year) (Mean ± SD)	28 ± 5.0		28 ± 4.1		27 ± 4.8		0.46
BMI (Kg/m^2) (Mean ± SD)	25.5 ±2.29		26 ± 2.0		26±2.58		0.45
Type of Infertility	N	%	N	%	N	%	0.11
Primary	22	44%	29	58%	32	64%	
Secondary	28	56%	21	42%	18	36%	
Duration of Infertility (Year)	3.2 ±1.4		3.26±1.8		3.7±2.2		0.33
Cause of Infertility	N	%	N	%	N	%	0.744
Unexplained	16	32%	17	34%	22	44%	
Male Factor	20	40%	21	42%	17	34%	
Female Factor	14	28%	12	24%	11	22%	

Table -3 shows other demographic features like days of induction from day 3 till HCG injection, number and diameter of dominant follicle on the day of HCG trigger and ET on the day of HCG trigger. This also shows no statistically significant difference between three groups. The RI and PSV values of perifollicular arteries show statistically significant difference between three groups (P-0.001).

Table 3:

	High Grade (Group A)	Mixed Grade (Group B)	Low Grade (Group C)	P Value
Days of induction Mean ± SD	10.5 ±3.58	11.5 ±2.29	11.0 ± 2.58	0.22

No. of follicles>18mm Mean ± SD	1.4 ±1.70				1.42 ±1.05				1.5±1.05				0.92
Diameter of follicles Mean ± SD	19.09±3.91				20.09±1.91				19.91±2.09				0.16
RI Mean ± SD	<.5		>.5		<.5		>.5		<.5		>.5		0.001
	44	88%	6	12%	33	66%	17	34%	4	8%	46	92%	
PSV (cm /s) Mean ± SD	>11		<11		>11		<11		>11		<11		0.001
	43	86%	7	14%	30	60%	20	40%	3	6%	47	94%	
ET (mm) Mean ± SD	9.5±1.36				9.86±1.0				9.6±1.2				0.30

Table -4 shows pregnancy rates in all 3 groups. In our study, 20 cases out of 150(13.33%) got pregnant. Out of 20 cases, 12 are from group-A (24%), 6 are from group-B (12%) and 2 are from groups-C (4%). This difference in pregnancy rate is statistically significant (P–0.0124) between the three groups.

Table 4:

	High Grade (Group A)		Mixed Grade (Group B)		Low Grade (Group C)		P Value
Pregnancy	N	%	N	%	N	%	0.0124
Negative	38	76%	44	88%	48	96%	
Positive	12	24%	6	12%	2	4%	

Discussion

IUI procedure is taken as first line ART treatment in some of the mild male and female factors of infertility despite of comparatively low success rate to IVF. Routinely the size of dominant follicle (DF>18mm) is taken as a criterion of maturity and so for HCG trigger. A relationship between perifollicular vascularity and chances of good quality oocyte and pregnancy has been reported since the early 1990's (7, 8) but its clinical value is not yet clear.

In this study, the overall pregnancy rate of IUI procedure in 150 cases, is 13.33%. The pregnancy rate in group -A ie high PFBF group is 24% (12 out of 50) in group – B ie mixed PFBF group is 12% (6 out of 50) and in group –C i.e low PFBF group is 4% (2 out of 50). This difference is statistically significant (P-0.0124). Our findings are comparable to Ray et al (15), whose overall pregnancy rate was 11.79% with 21% in group – I, 6.6% in group – II and 0% in group –III. Similarly Mad Kour et al (16) had total pregnancy rate of 8.88% with 20% in group 1, 6.7% in group 2 and 0% in group 3.

P.S. Bhal et al (17) observed the IUI cycles 36 hours after HCG administration and found that cycles with follicles of uniformly high-grade vascularity were associated with significantly higher pregnancy rate (31%) than cycles with mixed grade vascularity follicles (8%) (P- <0.05) with no pregnancy occurring in group with low grade vascularity. They also observed that mean age and duration of infertility were significantly higher (P-<0.05) in low grade vascularity group while the incidence of multiple pregnancies was twice as high in the group with high grade compared with mixed grade follicular vascularity (39% V/s 18%, P-NS). Early pregnancy loss rates were negatively correlated to the PFBF with the lower abortion rates being associated with high grade vascularity group (16% V/s 45%, P- NS). Amanda J.O' Leary et al (18) observed that in the group with high PFBF, the CPR was higher in women treated with u-gonadotropins compared with those treated with r-FSH (22.22% V/s 10.91%, P<.05) although the numbers were small. Ghazali et al (19) found that the follicles of high-grade vascularity were associated with higher pregnancy rate (group III = 19.5%) than cycles with low grade vascularity (group II = 12.5%) with no pregnancy occurred in group – I vascularity group. (P < .05). Early pregnancy loss rate was significantly higher in group – II follicular vascularity (33.3%) than group – III (12.5%) P. < 0.05.

Ragni et al (1) in her study of 318 women found pregnancy rate of 11.94% with no significant difference between low medium and high-grade vascularity groups, which were 14.11%, 10% and 11.8% respectively.

Shrestha et al (20) showed high grade ovarian PFBF in the early follicular phase during IVF was associated with higher clinical pregnancy rate. Huyghe et al (21) in their systematic review of 14 studies of ART cycles (both IVF and IUI) concluded that measuring PFBF could be a good prognostic marker for oocyte and embryo quality but even more for pregnancy rate after IVF/ICSI. This finding is not observed in studies concerning IUI.

This trend towards better perifollicular vascularity in women who got pregnant was demonstrated in previous studies (8, 11, 12, 13). The exact reason behind this difference is not clear. However, the quality and maturity of the oocyte depends on intrafollicular levels of oxygen and other nutrients 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. An association between poor PFBF and aneuploidy has been observed by a number of authors. Chui et al (12) demonstrated that occyte derived from follicles with low grade vascularity resulted in a significantly higher proportion of triploid embryos.

Similarly, Bhal et al (11). showed a significantly higher quality of mature oocytes and fertilization rate with significantly lower triploidy rate in the high-grade vascularity group. The compromised perifollicular blood flow leads to hypoxia responsible for aneuploid oocytes.

In our study low RI < .5 and high PSV > 11 cm/sec is associated with high grade vascularity in group A (88% and 86% respectively) while high RI>.5 and low PSV <11cm/sec is associated with low grade vascularity in group C (92% and 94% respectively). This difference of RI and PSV values of perifollicular arteries are statistically significant between three groups (P value 0.001). Low RI is associated with high PSV and high-grade perifollicular vascularity and thus the better quality of oocyte and pregnancy rate in group-A as compared to group- B & C. This finding is comparable to Sonal Panchal et at (14), whose study showed that when the perifollicular RI is > 0.53 and the PSV < 9cm/s, 12 hrs before HCG injection, the conception rates were only 10.76% and 14.2 % respectively as compared with 32.3 % and 27% respectively, when the perifollicular RI was <0.50 and the PSV was > 11cm/s. This shows that the follicles having oocytes capable of producing pregnancy have a perifollicular vascular network that is more uniform and distinctive.

Coulam et al (22) correlated peak systolic velocity (PSV) of individual follicles with oocyte recovery, fertilization rate and embryo quality in women undergoing IVF and ET. They observed that women who had PSV>10 cm/Sec. in at least one follicle on the day of HCG, more often became pregnant than those with PSV<10 cm/sec (P - <0.05). Nargund et al (23) demonstrated that there was a 70% chance of producing a grade 1 or 2 embryo if the PSV of PFBF was > 10 cm/sec compared with 14% if the PSV was < 10 cm/sec. Chui et al (12) failed to demonstrate any significant difference in the intra ovarian PI between those who conceived and those who did not.

Conclusion

In this study we used 2D PD which has its own limitations but it is more convenient and easily available so has a wider area of application with good predictive value for IUI cycle outcome. As there is low pregnancy rate in the group of women with uniformly low grade PFBF, the identification of these cycles would be valuable in terms of counseling with regard to the potential outcomes. Cancellation of such IUI cycles or non-conversion in to IVF cycle could be cost effective, both financially and emotionally. Since there were higher multiple pregnancy rates in stimulated IUI cycles with uniformly high grade PFBF, these cycles should be considered for follicle reduction or even cancellation.

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