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Can Follicular Output Rate (Fort) And Follicle Oocyte Index(Foi) Predict Live Birth Rate In Ivf/Icsi Cycles In Pcos ?

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ABSTRACT

Back groundPCOS (Polycystic ovarian syndrome) is characterised by anovulatory infertility, ART is prefered in case of Ovulation induction failure or resistance. Follicular Output Rate and follicle oocyte index are newer parameters proposed for predicting the outcome of controlled ovarian stimulation.

ObjectivesTo find out the association between different categories of FORT with clinical pregnancy rate and cumulative live birth rate, respectively and also to find out the association between different categories of follicle oocyte index with clinical pregnancy rate and cumulative live birth rate, respectively.

Material and methods The present study was retrospective observational study carried out in the Institute of reproductive medicine, Madras Medical Mission (MMM) hospital between 2020 and 2022 among women diagnosed with PCOS and had undergone IVF during the study period. Ethical clearance for the study was obtained from the institutional ethics committee. All the baseline and outcomes parameters were collected. FORT and FOI were calculated. ANOVA, Chi square test and logistic regression were applied. A P value of less than 0.05 was considered to be significant.

ResultsThe baseline characteristics were similar across different categories of FORT except for serum estrogen on the day of trigger. With regard to number of oocytes collected, number of MII oocytes, number of oocytes fertilised and number of embryos obtained were significantly more in the high FORT group than the middle and low group, respectively. FORT and FOI were found to be positively associated with one another. The proportion of cumulative clinical pregnancy and cumulative live birth were similar across different categories of FORT and FOI, respectively.

ConclusionFORT is an excellent predictor of ovarian responsiveness. Both the cumulative clinical pregnancy rate and cumulative live birth rate were found to be similar across different categories of FORT and FOI, respectively.

Key words PCOS, Follicles, Follicular output rate, Cumulative clinical pregnancy rate, live birth rate.

I. INTRODUCTION

Polycystic ovarian syndrome is characterised by hyperandrogenism, polycystic ovarian morphology and oligo-anovulation. PCOS in one of the main reasonfor anovulatory infertility in women of reproductive age group. The magnitude of such infertility was estimated to be 8 to 13%(1)(2)(3).In order to overcome the anovulatory infertility, assisted reproductive techniques were the main stay and In vitro fertilization (IVF) is one of the treatment options for them. Controlled ovarian stimulation is a vital step in IVF which involves induction of ovulation via administration of gonadotrophins during the menstrual cycle and aim of it was to obtain increased number of oocytes.

The controlled ovarian stimulation in PCOS usually results in production of poor-quality oocytes in higher proportion and also sometime lead to ovarian hyperstimulation syndromes (OHSS). Hence to adjust ovarian stimulation (OS), there are predictors like anti-mullerian hormone (AMH), antral follicle count (AFC) and basal follicle stimulating hormone (FSH), which were used to predict IVF outcome, but they had certain limitations(4)(5)(6)(7).One of the limitation is their ability to reflect follicular growth following exogenous gonadotrophin administration and their ability to determine the outcome following ART is also limited (8) (9).

In 2011, Genro et al introduced Follicular output rate (FORT) as a potential tool to evaluate follicular development. FORT is the ratio between pre-ovulatory follicle count on the trigger day (PFC) and antral follicle count (AFC)(10). Gallot et al reported a positive correlation between FORT and pregnancy outcomes and the study found high FORT values to have better pregnancy outcomes (11). Hassan et al reported that FORT was independently associated with clinical pregnancy rate among women who had unexplained infertility (12). Tan et al reported both clinical pregnancy rate and retrieval of high-quality embryos were associated with high FORT values and Yang et al reported a association between high FORT and cumulative live birth rate (13) (14).

Another parameter that has been proposed in the year 2018 was follicle oocyte index (FOI). It is defined as the ratio between number of oocytes retrieved and the antral follicle count(15). Poulain M et al reported a positive association between high FOI and high implantation rate. High FOI also resulted in high birth rate in the study (16). While some studies have reported no such association for FOI (17).

The present study was done to find out the association between different categories of FORT with clinical pregnancy rate and cumulative live birth rate, respectively and also to find out the association between different categories of follicle oocyte index with clinical pregnancy rate and cumulative live birth rate, respectively. Studies with similar objective were not done in the study setting before. The study will aid in adding evidence to find the appropriate parameter that could predict outcome of assisted reproductive technique.

II. METHODOLOGY

The present study was retrospective observational study carried out in the Institute of reproductive medicine, Madras Medical Mission (MMM) hospital between 2020 and 2022. The study was carried out among women diagnosed with PCOS and had undergone IVF here in the department of institute of reproductive medicine during the study period. Ethical clearance for the study was obtained from the institutional ethics committee. Total women who had undergone IVF for anovulatory infertility due to PCOS was 112. Since a retrospective study, data collected were from case sheets at the medical records department of the institution.

The data was collected using a semi structured proforma. The data recorded include age, BMI, menstrual history, type of infertility and years of infertility. Baseline values of LH, E2, AMH and AFC were recorded. The number cycles the participant had undergone with regard to ART was also recorded. The other factors recorded included the gonadotrophin dose used and duration of stimulation were also recorded. The type of trigger provided and PFC was noted down. With regard to the outcomes of controlled ovarian stimulation, variables like number of oocytes retrieved, MII oocytes collected, number of oocytes fertilized and number of embryos were recorded. Finally, whether the ART leaded to clinical pregnancy and live birth were made a note.

1.1. Procedure

The following protocol was followed for oocyte retrieval. The Controlled ovarian stimulation usually gets started on 2nd day of cycle using gonadotrophins (rFSH OR highly purified HMG) and fixed antagonist protocol with cetrorelix 0.25mg started from day 5 of stimulation until the day of trigger. When > 2 leading follicles reach 18mm, final oocyte maturation was triggered with dual trigger or HCG trigger. Oocyte retrieval done between 35-36 hours later.

1.2. Statistical analysis

The data collected were entered into Microsoft excel 2019 and the master chart was created. The master chart was then loaded onto SPSS version 26 for statistical analysis. The quantitative variables were expressed using mean and standard deviation. The qualitative or categorical variables using frequency and percentages. Based on the FORT values three groups were obtained namely, low (< 66.68), middle (66.68 – 89.02) and high (>89.02). Comparison of difference in the variables collected were made between the above said three categories. To compare the mean values between the three groups, ANOVA was used and to compare distribution of qualitative variable between the three groups, Chi square test was used. The FOI was also categorized into three categories with cutoffs at 0.626 and 0.822, respectively.

The odds ratio of clinical pregnancy rate and cumulative live birth rate for different categories of follicular output rate and follicle oocyte index, respectively was estimated using univariate logistic regression model. Multivariate logistic regression model adjusted for age, BMI, AMH and duration of infertility was also performed to find out the adjusted odds. A P value of less than 0.05 was considered to be statistically significant.

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III. RESULTS

The study included 112 women diagnosed with PCOS and undergone IVF. Based of FORT values, three groups were synthesised. They were low, middle and high. The mean age was found to be similar between the groups with P value of more than 0.05. The mean BMI was also found to be statistically similar between the groups.

With regard to menstrual history, 53.8%, 44.4% and 48.6% from the low, middle and high FORT, respectively reported irregular menstrual cycle. The proportion of irregular menstrual cycle was similar across the different categories of FORT with P value of more than 0.05. The distribution of type of infertility was also similar across the groups with a statistically insignificant P value. The mean year of infertility among the low group was 6.34 ± 3.12 years, middle group was 6.54 ± 3.78 years and the high group was 6.18 ± 2.88 years. The mean years of infertility was also similar between the groups with P value of more than 0.05.

The mean baseline LH value for the low group was 1.38 ± 1.03, for the middle group it was 1.65 ± 1.45 and that for the high group was 1.52 ± 1.27. The mean LH was similar across the groups with P value of more than 0.05. The mean E2 value at the baseline was higher in the high group (5721.57 ± 2823.96) followed by the middle group (4914.94 ± 2453.53) and finally the low group (3852.88 ± 2137.15). The mean were significantly different across the groups with P value of less than 0.05. The mean AMH values were similar between the groups but not the mean AFC count. The mean AFC count was 20.66 ± 6.99 in low group, 19.05 ± 6.44 in the middle and 16.73 ± 6.90 in the high group.

The GN dose used for low group was 4695.03 ± 1386.66, for middle category it was 4716.36 ± 1832.51 and for the high group was 4630.95 ± 1511.49. The mean was similar across the categories with P value of more than 0.05. The duration of stimulation was also found to be similar among low, middle and high FORD categories (P value > 0.05). With regard to the pattern of trigger, 59% had received dual trigger and 33.3% HCG in low category, 77.8% dual trigger and 16.7% HCG in the middle category and 81.1% dual trigger and 16.2% HCG in the high category. The distribution was similar across the groups with P value of more than 0.05. The mean PFC for the low category was 10.77 ± 3.95, for the middle category it was 15.03 ± 4.88 and for the high category it was 19.57 ± 6.97. The mean PFC was higher in the high group followed by middle and low groups and the difference was significant with P value of less than 0.05 (Table 1).

Table 1: Patient baseline characteristics.

FORT		Low (<66.68) n=39	Middle (66.68 - 89.02) n=36	High (>89.02) n=37	F/X^2	P value
Age (years)		30.82 ± 4.62	31.53 ± 4.15	30.70 ± 4.34	0.378	0.686
BMI (Kg/m^2)		29.62±5.30	28.22±4.35	28.96±4.87	0.770	0.465
Menstrual History	Irregular	21(53.8)	16(44.4)	18(48.6)	0.667	0.717
	Regular	18(46.2)	20(55.6)	19(51.4)		
Years of infertility (years)		6.34±3.12	6.54±3.78	6.18±2.88	0.106	0.900
Type of infertility	Primary	26(66.7)	18(50)	23(62.2)	2.28	0.318
	Secondary	13(33.3)	18(50)	14 (37.8)		
LH on trigger day(IU/l)		1.38±1.03	1.65±1.45	1.52±1.27	0.445	0.642
E2 trigger day(pg/ml)		3852.88±2137.15	4914.94±2453.53	5721.57±2823.96	5.375	0.006
AMH (ng/ml)		4.56±2.41	4.73±2.24	4.92±2.37	0.223	0.801
No of AFC		20.66±6.99	19.05±6.44	16.73±6.90	3.199	0.045
GN dose		4695.03±1386.66	4716.36±1832.51	4630.95±1511.49	0.029	0.971
Duration of stimulation		10.77±1.01	10.81±0.951	10.89±0.96	0.157	0.855
Trigger	Agonist	3(7.7)	2(5.6)	1(2.7)	5.640	0.228
	Dual trigger	23(59)	28(77.8)	30(81.1)		
	HCG	13(33.3)	6(16.7)	6(16.2)		
PFC		10.77±3.95	15.03±4.88	19.57±6.97	25.19	0.001*
FORT		52.70±12.09	79.34±6.67	123.46±54.05	46.86	0.001*

*Statistically significant.

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With regard to the number of oocytes collected, the mean was 11.49 ± 4.62 in the low group, 14.25 ± 4.67 in the middle and 16.49 ± 8.21 in the high group. The number of oocytes were significantly different across the groups with P value of less than 0.05. Similar pattern was found among the number of MII oocytes collected. The mean number of fertilized oocytes was 10.57 ± 4.64 in the high group, 9.78 ± 3.99 in the middle group and 8.08 ± 3.63 in the low group. The difference was also statistically significant with P value of less than 0.05. The mean FOI for the low group was 0.56 ± 0.17, for the middle group it was 0.75 ± 0.17 and for the high group it was 1.04 ± 0.60. The difference in FOI was also statistically significant. For all the above variables, the mean was higher in high group followed by middle and lower groups.

Table 2: Patient's laboratory indicators and clinical outcomes.

FORT		Low (<66.68) n=39	Middle (66.68 - 89.02) n=36	High (>89.02) n=37	F/X^2	P value
Number of oocytes collected		11.49±4.62	14.25±4.67	16.49±8.21	6.496	0.002*
MII oocytes collected		9.54±3.85	11.61±4.59	12.51±5.63	3.961	0.022*
Number of oocytes fertilized		8.08±3.63	9.78±3.99	10.57±4.64	3.669	0.029*
Number of embryos		7±3.61	8.92±3.96	9.24±4.48	3.462	0.035*
Follicle Oocyte Index (FOI)		0.56±0.17	0.75±0.17	1.04±0.60	15.016	0.001*
Follicle Oocyte Index (FOI)	<0.626	26(66.7)	5(13.9)	8(21.6)	44.31	0.001*
	0.626-0.822	11(28.2)	19(52.8)	6(16.2)		
	>0.822	2(5.1)	12(33.3)	23(62.2)		
Cumulative Clinical pregnancy rate	Positive	21(53.8)	20(55.6)	23(62.2)	0.591	0.744
	Negative	18(46.2)	16(44.4)	14(37.8)		
Cumulative live birth rate	Yes	15(38.5)	18(50)	22(59.5)	3.367	0.186
	No	24(61.5)	18(50)	15(40.5)		

*Statistically significant

The cumulative clinical pregnancy rate was 53.8%, 55.6% and 62.2% in the low, middle and high FORT groups, respectively. The proportion were similar across the groups with P value of more than 0.05. The cumulative live birth rate was 38.5%, 50% and 59.5% for the low, middle and high groups, respectively. The proportion of cumulative live births were also found to be similar across different categories of FORT with P value of more than 0.05 (Table 2).

Table 3: Patient's laboratory indicators and clinical outcomes with regard to FOI.

FOI		<0.626 (n=39)	0.626-0.822 (n=36)	>0.822 (n=37)	F/X^2	P value
Cumulative Clinical pregnancy rate	Positive	24(61.5)	19(52.8)	21(56.8)	0.590	0.745
	Negative	15(38.5)	17(47.2)	16(43.2)		
Cumulative live	Yes	20(51.3)	15(41.7)	20(54.1)	1.234	0.540

birth rate	No	19(48.7)	21(58.3)	17(45.9)		

The cumulative clinical pregnancy rate was 61.5% among those with FOI of < 0.626, 52.8% among those with FOI of 0.626 to 0.822 and 56.8% among those with FOI of >0.822. The proportion of cumulative pregnancy rate was similar across the categories with P value of more than 0.05. For cumulative live births, the proportions were 51.3%, 41.7% and 54.1% for groups FOI < 0.626, FOI 0.626 to 0.822 and FOI > 0.822, respectively. The cumulative live births were similar across the different categories of FOI with P value of more than 0.05 (Table 3).

With regard to regression models, both univariate and multivariate logistic regression revealed similar odds ratios for cumulative clinical pregnancy rate and cumulative birth rate for different categories of FORT. With regard to FOI too, both non adjusted and adjusted odds ratio were similar across the categories in relation to cumulative clinical pregnancy rate and cumulative live birth rate, respectively (Tables 4,5,6,7).

Table 4: Follicular output rate and cumulative clinical pregnancy rate.

	Non adjusted		Adjusted	
FORT	OR(95% CI)	P value	OR (95% CI)	P value
Low	1		1	
Middle	1.071 (0.431-2.662)	0.882	1.130(0.440-2.903)	0.799
High	1.408 (0.564-3.517)	0.464	1.370(0.534-3.516)	0.513
Adjusted for age, BMI, AMH and duration of infertility				

Table 5: Follicular output rate and cumulative live birth rate.

	Non adjusted		Adjusted	
FORT	OR(95% CI)	P value	OR (95% CI)	P value
Low	1		1	
Middle	1.600(0.639-4.007))	0.316	1.771 (0.678-4.626)	0.243
High	2.347(0.935-5.890)	0.069	2.370(0.912-6.159)	0.077
Adjusted for age, BMI, AMH and duration of infertility				

Table 6: Follicle oocyte index and cumulative clinical pregnancy rate.

	Non adjusted		Adjusted	
FOI	OR(95% CI)	P value	OR (95% CI)	P value
<0.62	1		1	
0.62-0.81	0.699(0.279-1.751)	0.444	0.740(0.282-1.944)	0.541
>0.81	0.820(0.328-2.050)	0.672	0.824(0.321-2.112)	0.687
Adjusted for age, BMI, AMH and duration of infertility				

Table 7: Follicle oocyte index and cumulative live birth rate.

	Non adjusted		Adjusted	
FOI	OR(95% CI)	P value	OR (95% CI)	P value
<0.62	1		1	
0.62-0.81	0.678(0.272-1.691)	0.405	0.698(0.264-1.843)	0.468
>0.81	1.118(0.454-2.752)	0.809	1.132(0.446-2.875)	0.794
Adjusted for age, BMI, AMH and duration of infertility				

IV. DISCUSSION

PCOS was found to be associated with anovulatory infertility among women in the reproductive age group and assisted reproductive techniques were one method relied up on to overcome the infertility. Controlled ovarian stimulation is one of the vital steps of IVF (1)(2)(4)(5). To predict the outcome of COS, AMH, AFC and FSH were monitored (6). Follicular Output Rate and follicle oocyte index were newer parameters proposed for predicting the outcome (13)(15). The present study was done with objective of finding the association between the above said factors and cumulative clinical pregnancy rate and cumulative live birth rate, respectively.

The present study was retrospective observational study carried out in the Institute of reproductive medicine, Madras Medical Mission (MMM) hospital between 2020 and 2022. The study was carried out among 112 women diagnosed with PCOS and had undergone IVF here in the department of institute of reproductive medicine during the study period. Ethical clearance for the study was obtained from the institutional ethics committee.

The baseline characteristics of the three groups of FORT formed in the study, namely low, middle and high were similar except for the serum estrogen on the day of trigger values. The above indicate the three groups formed were similar in characteristics. The present study revealed similar AMH levels across various categories of FORT. Hassan et al also reported a similar result where the mean AMH values across different categories had been similar(12). In contrast to the present study Estradiol values were similar across different categories of FORT in study by Genro VK et al (10).

1.3. Laboratory indicators and clinical outcomes

Number of oocytes collected were found to be more in the high FORT group than in the middle and low FORT groups in the present study. Similar pattern was also observed with regard to MII oocytes collected, Oocytes fertilized and number of embryos obtained. Similar results were described by Grynberg M and Labrosse J.(10) The latter study stated FORT to be effective tool to determine ovarian responsiveness to gonadotrophins (18). To arrive at the above conclusion three studies were looked up on Gallot et al (11), Hassan et al (12) and Zhang et al (19)

The present study also found that the high FORT group had high FOI values followed by the middle FORT group and low FORT group, respectively. Chen L et al also reported a similar relationship between FORT and FOI. They had also stated the relationship to be consistent (20).

1.4. Association of FORT and FOI with cumulative clinical pregnancy rate

For both FORT and FOI categories, the proportion of cumulative clinical pregnancy rate was similar and no significant difference were found between them. Both univariate and multivariate regression in the present study also revealed similar results with non-significant odds ratios. Gallot V et la reported a contrast result to the present study where the proportion of cumulative clinical pregnancy increased with increase in the FORT category (11). Jiang et al reported that high FORT was associated with increased cumulative clinical pregnancy rate (21). Li P and Chen Z reported clinical pregnancy to be high among participants with high FOI than those with low FOI (22).

1.5. Association of FORT and FOI with cumulative live birth rate

For both FORT and FOI categories, the proportion of cumulative live birth rate was similar and no significant difference were found between them. Both univariate and multivariate regression in the present study also revealed similar results with non-significant odds ratios. In contrast to the present study Jiang et al reported high FORT to be associated with high cumulative live birth rate than low FORT (20).

V. STRENGTH AND LIMITATION

The limitations of the study were that it was a single centre study. A multicentre study would have yielded more generalisable results. Most variable used in the study were objective rather than subjective there by decreasing the chance for information bias. Finally the sample size in the study was limited by the duration of the study.

VI. CONCLUSION

FORT is an excellent predictor of ovarian responsiveness. Both the cumulative clinical pregnancy rate and cumulative live birth rate were found to be similar across different categories of FORT and FOI, respectively.

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