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Does the size of antral follicle matter? Relation of FORT to follicular diameter in stimulation protocol

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A B S T R A C T

Background: This study aimed to investigate whether the diameter of antral follicles, specifically comparing those with diameters of 6 mm or less (AFC≤6) versus those greater than 6 mm (AFC > 6), can predict ovarian responsiveness, as assessed by the Follicular Output Rate (FORT) in women undergoing IVF treatment.138 women with regular menstrual cycles and no ovarian abnormalities, undergoing controlled ovarian hyperstimulation (COH) were included in this study. Number and size of antral follicles were noted on day 2 of cycle. Number of pre ovulatory follicles were noted and FORT was calculated on day of trigger with HCG. The correlation among FORT with age, AFC ≤ 6, AFC > 6, number of oocytes, body mass index (BMI), and anti-Mullerian hormone (AMH) were also assessed.

Result: The mean age of the women was 31.36 (± 3.28) years, the mean FORT was 53.453. We found positive correlation between the FORT and antral follicles with diameter ≤6mm (r= 0.467, P <0.001) and an inverse correlation between the FORT and antral follicle > 6mm in diameter (r = − 0.436, P<0.001).

Conclusion: Ovarian responsiveness, as indicated by the Follicular Output Rate (FORT), was positively correlated with the presence of smaller antral follicles (AFC ≤6mm).

Keywords: FORT, Ovarian responsiveness, Antral follicular diameter.

INTRODUCTION

Ovarian responsiveness is one of the most commonly studied parameters in clinical research concerning In Vitro Fertilization treatment.[1] The prediction of ovarian response , which is evaluated through ovarian reserve is fundamental for both prognosis and treatment individualization.[2] Monitoring and assessing ovarian responsiveness helps in tailoring IVF protocols to individual patients, optimizing stimulation regimens, and ultimately improving the chances of successful pregnancy. Treatment individualization is key in optimizing IVF outcomes. Selecting the appropriate gonadotrophin-releasing hormone (GnRH) analogue protocol and the initial gonadotrophin dose is essential to achieve an ideal ovarian response.

This careful tailoring helps avoid both low and hyper responses, which can lead to cycle cancellation and increased costs. For poor responders, the ideal ovarian reserve test should be able to identify women whose chances of pregnancy would be so diminished that it would be inappropriate to submit them to the potential adverse effects of exogenous gonadotrophin stimulus.

Antral follicle count and anti- Mullerian hormone have begun to dominate the clinical scene. Both AMH and AFC have a good discriminatory capacity to predict poor or high response in IVF. [3] These have been used for predicting ovarian response and for creating an individualized dose adjustment , but recent studies have shown that AFC alone is not a reliable marker for prediction of ovarian response and treatment individualization. The ovarian response may be inadequate even in patients with normal AFC and anti mullerian hormone levels.

Antral follicular size could be an additional valuable predictive marker other than antral follicular count in predicting ovarian response. The distinction of various size categories maybe relevant since various studies show that endocrine function of a follicle is related to its diameter.[4]

The **Follicular Output Rate (FORT)** is a clinical measure used to assess ovarian responsiveness, specifically in the context of fertility treatments like in vitro fertilization (IVF). It is essentially a way of quantifying how well the ovaries respond to stimulation. The Follicular Output Rate (FORT) evaluates the proportion of follicles that were responsive to FSH.

FORT is calculated as the ratio of the number of oocytes retrieved during an ovarian stimulation cycle to the number of antral follicles (AFCs) present at the baseline (typically measured on Day 2 of the menstrual cycle). Assessing ovarian sensitivity to FSH with FORT and understanding mechanisms behind hypo-response in ART opens new possibilities in the treatment of hypo-responders.[5]

Despite several studies having demonstrated a significant predictive value for antral follicular count in the ovarian response rate and pregnancy rates of patients undergoing IVF treatment, there are very few reports in the literature about the predictive value of antral follicular size in ovarian responsiveness, and none of them have used FORT as a measure of responsiveness. This study was designed to evaluate the correlation between antral follicle diameter and FORT in women under controlled ovarian hyper stimulation for assisted reproductive techniques. Main objective of this study was to evaluate whether the pool of follicles up to 6 mm or larger than 6 mm correlates better with the ovarian response to the controlled stimulus.

MATERIALS AND METHODS

We prospectively studied 138 patients, ranging from 26 to 45 years of age, who underwent COH for IVF + embryo transfer (ET) from December 2022 to December 2023. All of the patients met the following inclusion criteria: Both ovaries were present, without any morphological abnormalities, and seen adequately on transvaginal ultrasound. The exclusion criteria were: current or past diseases affecting the ovaries , clinical and/or biological signs of hyperandrogenism, diagnosis of polycystic ovarian syndrome.

Local institutional review board approvals for the use of clinical data for research studies were obtained and written informed consent was obtained from all patients.

The antral follicle size and count assessments were performed with 7.5 to 10 MHz transvaginal probe sonoscape, on Day 2/3 of cycle. Baseline AFC count was recorded and number of follicles of diameter 6mm or less (AFC6) and those with diameter more than 6mm(AFC>6) were noted. Patients were subjected to controlled ovarian hyperstimulation from day2/ day3. The gonadotrophin FSH was started in dose of 225 IU. Follicular monitoring was done from day 6, whenever 1 follicle was found to be in size more than 14mm, antagonist injection cetrorelix 0.25mg subcutaneously was given daily. Follicle monitoring was continued. When more than 2 preovulatory follicles were seen, Follicular Output Rate(FORT) was calculated according to formula given below.

$$\text{FORT} = \frac{\text{Number of pre ovulatory follicles on HCG day}}{\text{number of AFC at baseline}} \times 100$$

10000 IU Human Chorionic Gonadotropin was administered as soon as more than 2 preovulatory follicles (16 to 22mm in diameter) were seen.Oocytes were retrieved by transvaginal ultrasound guided aspiration 36 hrs after HCG administration.Then, number and grading of oocytes was calculated.Number of embryos formed and quality of embryos were noted.Embryo transfer was performed on day 3/5 according to embryo development.Beta HCG was done after 15 days.Chemical pregnancy, which is a positive urinary pregnancy test was noted.Clinical pregnancy, defined as presence of intrauterine embryo with cardiac activity at around 6 weeks after treatment was noted.

Mean and standard deviation were used to describe quantitative data, and frequency and percentage will be used for qualitative data. The relationship between two continuous variables was assessed by a correlation analysis when they were independent from each other and by regression when there was a dependent relationship between the variables. Spearman's test was used to determine if the correlation coefficients (r) were significantly different from zero. The level of significance was kept 95% for all statistical analysis.

RESULTS

This study was done on 138 women. The demographic and reproductive data are summarized in Table 1. Based on this table, the mean age of patients was 31.36 ± 3.28. Mean BMI, and AMH were 21.38±1.39 Kg/m^2 and 2.39 ±1.29 ng/mL respectively. The mean of FORT (%), AFC ≤ 6, AFC > 6, and the number of oocytes was 53.45±19.83, 8.32±3.38 , 2.81±2.83, and 5.45± 2.80, respectively.

Table 1 : The demographic and reproductive data

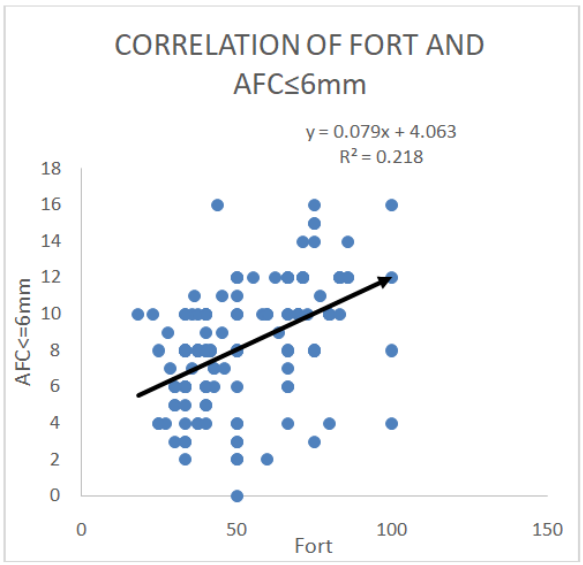
Variable	Mean ± SD
Age	31.36 ± 3.28
FORT (Follicular Output Rate) (%)	53.45±19.83
Total AFC (antral follicle count)	11.29 ± 3.73
AFC ≤ 6	8.32±3.38
AFC > 6	2.81±2.83
Number of oocytes retrieved	5.45± 2.80
Number of embryos formed	3.95± 2.11
BMI (body mass index) Kg/m^2	21.38±1.39
AMH (anti-Mullerian hormone) ng/ml	2.39 ±1.29

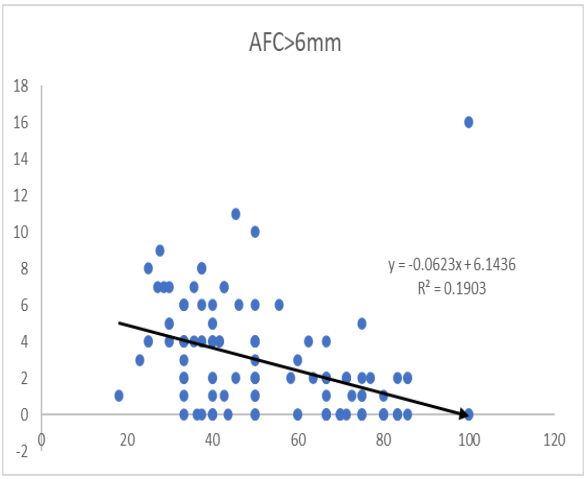
The indications for IVF-ET were unexplained infertility (28.26 %) , tubal factor (26.08%), male factor (15.94%), ovarian factor (15.94 %) and multiple causes (8.71%).

The correlation between FORT and other related variables is shown in Table 2. Based on this table, there was a significant correlation between FORT and AFC > 6, AFC≤6, number of oocytes retrieved and number of embryos formed($P < 0.05$). Other related variables (BMI, age, AMH) had no significant correlation with FORT ($P > 0.05$).

Table 2 Correlation among FORT (Follicular Output Rate) and other related variable

Variables	Correlation coefficient	P value
Age	0.013	0.879
BMI	-0.011	0.890
AFC≤6	0.467	<0.001
AFC >6	-0.436	<0.001
AMH	0.035	0.682
Number of oocytes	0.655	<0.001
Number of embryos	0.0053	<0.001

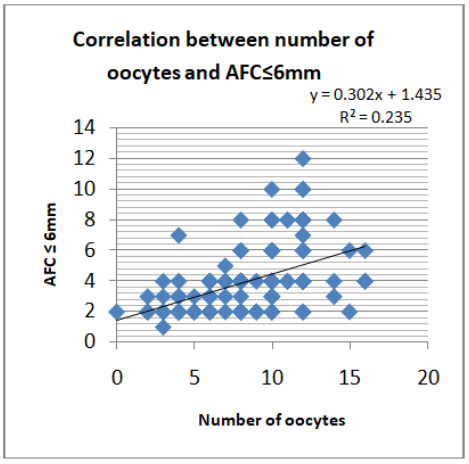




Both AFC≤ 6mm and AFC >6mm correlated positively with number of oocytes retrieved as shown in table 3. This correlation was statistically significant forAFC≤6mm and not for AFC >6mm.

Table 3 Correlation among number of oocytes retrieved and AFC≤6 and AFC>6

Variable	Correlation coefficient	P value
AFC≤6mm	0.6446	P < 0.005
AFC>6mm	0.0489	P >0.005



DISCUSSION

Our study focused on examining the relationship between antral follicular diameter and Follicular Output Rate (FORT) in women undergoing controlled ovarian hyper stimulation for assisted reproductive technology (ART). FORT was used as a tool to assess ovarian responsiveness. Some studies recognized AFC and AMH as significant predictors of ovarian response.[3,6] Previous studies have indicated that there is a positive relationship between the Follicular Output Rate (FORT) and the outcomes of in vitro fertilization (IVF).[7,8] Fewer studies have delved into the correlation between FORT and various demographic factors, related variables, and antral follicle size in ovarian responsiveness. Our study showed that there was no significant correlation of FORT with age and BMI. Similar results were shown by Bessow et al[4] and Mardanian et al[9]. Our study showed higher FORT was associated with higher chances of positive pregnancy outcomes. Those with Positive pregnancies had much higher FORT levels (74.025) than those with Negative pregnancies (38.975) and this result was statistically significant. We observed that patients with a higher FORT had a greater number of antral follicles (AFCs) measuring ≤6mm at baseline on day 2 of the menstrual cycle. Conversely, the group with low FORT had a higher proportion of AFCs greater than 6mm in size. The number of oocytes retreived , number of embryos formed and clinical pregnancy rate were positively correlated with the number of AFC ≤6mm and this correlation was statistically significant. AFC>6mm was negatively correlated with clinical pregnancy rate. However Bessow et al showed results opposite to ours and in their study AFC >6mm were positively correlated with FORT [4]. While Mardanian et al did not find much difference in the correlation between the AFC ≤ 5 and AFC > 5, and both positively correlated with the number of MII oocytes retrieved.[9]

CONCLUSION

Our study evaluated correlation between FORT and antral follicular diameter , the results suggest that ovarian responsiveness, as indicated by the Follicular Output Rate (FORT), is positively correlated with the presence of smaller antral follicles (AFC ≤6mm). These smaller follicles might represent a pool that is more receptive to FSH (Follicle Stimulating Hormone) stimulation. It highlights the potential for this correlation to enhance predictions of ovarian responsiveness and allow for more individualized treatment strategies for patients undergoing controlled ovarian hyperstimulation (COH). Verification through a clinical trial is recommended to further validate these finding.

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